A PATHOLOGICAL STUDY OF THE PATHWAYS OF INFECTION TO THE INTRACRANIAL STRUCTURES FROM FOCI OF INFLAMMATION ON THE FACE AND IN THE NASAL AND NASAL ACCESSORY CAVITIES.

A PATHOLOGICAL STUDY OF THE PATHWAYS OF INFECTION TO THE INTRACRANIAL STRUCTURES FROM FOCI OF INFLAMMATION ON THE FACE AND IN THE NASAL AND NASAL ACCESSORY CAVITIES.

Thesis submitted to the University of Edinburgh for the Degree of Doctor of Medicine

by

FRANCIS ESMOND REYNOLDS,
M.B., Ch.B., Edin., D.T.M.& H.Camb., etc.

1930.

To

A. LOGAN TURNER,
M.D., LL.D., F.R.C.S.E.,

my Friend, my Former Chief, and
my Present Fellow Worker

This Thesis
is dedicated.

CONTENTS.

A PATHOLOGICAL STUDY OF THE PATHWAYS OF INFECTION TO THE INTRACRANIAL STRUCTURES FROM FOCI OF INFLAMMATION ON THE FACE AND IN THE NASAL AND NASAL ACCESSORY CAVITIES.

I. INTRODUCTION.

Having occasion some twenty years ago to study the literature of acute infection of the leptomeninges from inflammatory foci in the nose, nasal accessory sinuses, and pharynx, the writer was much impressed by the fact that in almost every case published in which the author had mentioned the pathway by which the infection had passed from the peripheral focus to within the cranium, the lymphatic system either was stated to be the route or it was suggested that this was the path involved.

Equally remarkable was it that in the numerous cases which had been studied up to that time, no attempt had been made to demonstrate microscopically the pathway of infection.

Moreover, a direct continuity between the lymphatic vessels of the peripheral parts and the

intradural structures was unknown to anatomists. A lymphatic system begins in the dura mater and drains through various of the foramina in the base of the skull into the deep cervical lymph nodes; this system is closed, however, on the inner side having no communication with the pia-arachnoid spaces.

By injection experiments in rabbits, Key and Retzius had shewn that the olfactory nerve filaments situated in the nasal mucous membrane over an area occupying the upper third of the septum and nearly the whole of the opposed superior turbinal or concha were surrounded by sheaths which were directly continuous above with the pia-arachnoid spaces. In 1905 Cunéo and André demonstrated that the same anatomical arrangement existed in the human subject, and this was confirmed some years later by Zwillinger.

Although these perineural sheaths are referred to frequently as "lymph sheaths", this nomenclature, as Le Gros Clark has recently pointed out, is not correct since there is no evidence that they contain lymph.

Further, the central nervous system does not possess lymphatic vessels in the ordinary acceptance of the term. The lymph drain of the brain and spinal cord is effected by way of the perivascular spaces

(Virchow Robin spaces); these are formed by prolongations of the pia mater and are carried, so to speak, into the substance of the brain and cord by the ingrowth of the blood vessels during early development. They are continuous with the pia-arachnoid spaces and hence the waste products of metabolism of both the nervous parenchyma and its supporting interstitial cells are eliminated into the cerebrospinal fluid and reach the venous channels through the Pacchyonian bodies.

Not only had it been shewn that the pia-arachnoid spaces were directly continuous with the perineural sheaths of the olfactory nerve filaments, but it was a well established fact that the optic nerve was surrounded by a prolongation of the pia-arachnoid membrane. Further, it had been proved that the perilymph of the inner ear was in direct continuity with the cerebrospinal fluid through the aqueduct of the cochlea.

Along no other structures has it been demonstrated that the cerebrospinal fluid is in direct communication with parts outside the skull.

A further observation of importance to the subject was made as a result of the injection experiments of Cunéo and André referred to above. These investigators found that the injection material

passed from the pia-arachnoid spaces not only into the olfactory perineural sheaths but also into the superficial lymphatic network of the olfactory mucous membrane. From these experiments they concluded that they had demonstrated continuity not only between the meningeal spaces and the olfactory nerve sheaths but also between the meningeal spaces and the lymphatic network of the olfactory nasal mucosa. On developmental and anatomical grounds, however, it seems more probable that the injection did not enter the mucosal lymphatic network directly through foramina in the cribriform plate, but that it percolated from the perineural spaces through the tissue spaces into the lymphatic vessels of the mucous membrane.

In 1893, Sir William Macewen published his classical work on "Pyogenic Infective Diseases of the Brain and Spinal Cord". Although microscopical changes were not studied, from the wealth of anatomical and clinical detail, of careful macroscopic studies made both during life and at autopsy and of his reasoned deductions of the pathological processes, the book marks an epoch not only in the pathway of intracranial infection but in cranial surgery.

During the subsequent two decades, the knowledge in regard to the route of infection of the intracranial structures from foci of inflammation in the

face, nose, nasal accessory sinuses and pharynx remained much as has been indicated above. Numerous cases were reported in the literature and without doubt many others occurred both in private and hospital practice which were not published. In the instances recorded in literature, with the few exceptions mentioned below, no attempt was made to trace by actual microscopical demonstration the path by which the infection had reached the intracranial structures. To judge from the literature, it seems that it was accepted that the route was by the "lymphatics".

The papers, six in number, which appeared before the investigation of the present series was commenced and which recorded microscopical search for the pathway of infection are as follows:-

In 1890, Ortmann published the case of a boy who died of cavernous blood sinus thrombosis and leptomeningitis secondary to suppuration in the sphenoidal air sinuses. Microscopically, diplococci were demonstrated in the sphenoidal mucosa, in the osseous walls of these air cavities and in the leptomeninges. From these facts the author concluded that the infection of the meninges occurred by direct continuity, the micro-organisms passing from the sphenoidal cavity to the bone, giving an osteitis, and thence spread to

the meninges.

In 1906, Hajek recorded the case of a young woman who developed acute purulent leptomeningitis secondary to an intranasal operation for purulent ethmoiditis. At autopsy, osteomyelitis was found in the roof of one of the ethmoidal air cells, and streptococci were demonstrated microscopically in the inflamed ethmoidal mucosa and in the diploic blood spaces. The author concluded that infection of the leptomeninges arose by direct spread through the bone.

In 1908, von Eicken, in a fatal case of leptomeningitis consecutive to an operation on the frontal sinuses, demonstrated pus in the olfactory perineural sheaths, the micro-organisms having apparently gained entrance to these structures at the margin of the cut edge of the middle turbinal, which had been removed at the operation. From this he concluded that infection had reached the leptomeninges by way of the olfactory perineural sheaths.

In 1911, Miodowski demonstrated a similar route of infection in a patient who had died of acute purulent leptomeningitis supervening on submucous resection of the nasal septum performed according to the method of Killian. Further, by means of serial sections, he shewed that the pus in the olfactory perineural sheaths was continuous with that in the pia-arachnoid

spaces.

In 1911, Manasse published a case in which acute inflammation in the ethmoidal air cells gave rise to an extra- and intra-dural abscess. Microscopically, the small blood vessels of the involved portion of the dura mater were filled with pus and septic thrombi. From this he concluded that the infection had passed to the intra-dural structures by progressive thrombosis of the dural veins.

In 1923, Sternberg recorded four cases of leptomeningitis, one of which was consequent upon chronic ethmoiditis, and three were the result of acute frontal sinus inflammation. In three of these cases, septic thrombi were demonstrated microscopically in the perforating veins of the bone, while in the fourth case, one of acute frontal sinusitis, no changes were found in the posterior osseous wall of the air sinus. Sternberg concluded that in these cases the infection had been carried from the air cavity to the meninges by the perforating veins.

Hence, since 1890, so far as the writer has been able to find, the literature contains only nine cases of intracranial complication from primary foci of inflammation in the nose or nasal accessory sinuses in which an attempt has been made to demonstrate microscopically the actual pathway of infection.

Except in the cases published by von Eicken and Miodowski, the material examined was too limited in extent to exclude other routes of infection and, from experience gained by the investigation of the series of cases now recorded, the conclusions drawn from the pathological changes cannot be accepted as being justified or probable.

If a fact is demonstrable, science demands that it must be made manifest. In 1922, Dr Logan Turner, F.R.C.S.E., and I decided, therefore, to obtain material from a series of fatal cases of intracranial infection secondary to a focus of inflammation in the face, nose, or nasal accessory sinuses, and in each instance attempt to demonstrate by microscopical preparations the actual path by which the infection had reached the intracranial structures. By ascertaining the natural pathway in man in disease it was obvious that any fallacies which might arise in experimental work on lower animals or on the human cadaver would be avoided. Further, we hoped to ascertain some of the factors underlying the process of intracranial infection. Although confining our research to cases in which the primary focus was on the face and in the nasal and nasal accessory sinuses it must be understood that processes essentially the same as we have shewn here are responsible for intra-

cranial complications of neighbouring peripheral inflammatory foci situated elsewhere. While pursuing our investigations, a large amount of material has become available to us and we have been able to demonstrate that pathologically the whole scalp has a relationship to the intracranial structures similar to that which the face, nose and nasal accessory sinuses have to the dura mater, leptomeninges cavernous blood sinuses and brain in the anterior part of the cranial cavity. The only pathology "special" to the area selected for the research depends solely upon the particular anatomical features of this part of the body as contrasted with those of any other part.

The portion of the research which deals with the morbid histology and the pathological processes involved forms the subject of the present Thesis. In addition, Dr Logan Turner has kindly allowed me to use material collected by him and at present in the Museum of the Ear, Nose and Throat Department of the Royal Infirmary, Edinburgh, to illustrate certain macroscopic pathological changes.

Since 1922, when the investigation of the present series of cases was begun, a certain number of papers have been published which record the result of microscopical examinations undertaken to

elucidate the pathway by which intracranial structures have been infected from foci of inflammation in the nasal accessory sinuses and in the ear, two cases of the latter category having an intimate bearing on the present Thesis.

In 1926, H. Burger recorded the case of a young girl who died of septic thrombosis of the cavernous sinuses following upon chronic inflammation of the sphenoidal air sinuses. Microscopically, the air sinuses were undergoing their normal enlargement by the process of pneumatisation of the bone. The mucous membrane was inflamed, however, and infiltrated by polymorphonuclear leucocytes. Infected veins were traced from the inflamed mucosa into the neighbouring bone marrow which was found also to be infected. Further, on the cranial side infected veins were traced from the bone marrow to the cavernous blood sinuses, the latter structures being filled with septic clot. From these data, Burger concluded that the veins of the sphenoidal mucosa had become the site of a primary septic thrombosis and that the infection had reached the cavernous blood sinuses by an extension of the thrombotic process along the veins into the diploic blood spaces and thence along diploic veins to the cavernous sinuses.

In the same year, 1926, H. Brunner recorded a series of five cases of septic thrombosis of the cavernous blood sinus complicating suppuration in the ear. Although the title of the present writer's study is confined to infection of the intracranial structures from inflammatory foci on the face and in the nose and nasal accessory simuses, the whole progress of infection of the cavernous blood sinus can be understood only if certain cases of otogenous origin are considered (see pg.178). Of Brunner's series of cases, two (Cases I and IV) are of especial interest in connection with the present Thesis. Both were cases of chronic otitis media with purulent infiltration of the inner ear. The mucous membrane of the Eustachian tube was inflamed and abscesses were present in the subepithelial connective tissue; the bony wall between the tube and the carotid canal was affected in places, the veins of the carotid plexus were filled by septic thrombi, and the connective tissue was infiltrated by pus. From these data, the author concluded that in both cases the infection had passed by direct extension from the Eustachian tube through the bone and into the carotid canal; that septic thrombosis of the veins forming the carotid venous plexus had occurred there, and the thrombus had extended into the

cavernous blood sinus.

In 1929, J. G. Druss recorded two cases of intracranial complications associated with disease of the sphenoid bone. The first case was that of a woman, aged 52, who developed acute purulent leptomeningitis secondary to infection of the persistent buccal portion of the cranio-pharyngeal canal, and the second was that of a frontal lobe abscess consequent upon chronic sphenoiditis; in the latter case the abscess arose by direct extension.

In conclusion, I wish to express my thanks to the various Clinicians who have given me access so freely and generously to the material required; to the Assistants in the Pathological Department of the Royal Infirmary, Edinburgh, for their help in obtaining material; to Professor T. J. Mackie, M.D., and Dr W. R. Logan, F.R.C.P.E., for valuable assistance in elucidating and demonstrating various pathological data; and to Professor Lorrain Smith, F.R.S., for useful advice and helpful criticism. It would be presumptuous on my part to express appreciation of the patience, thoroughness, sound judgment and true scientific spirit of my fellow-worker, Dr Logan Turner, F.R.C.S.E.; to him I dedicate this Thesis.

II. GENERAL CONSIDERATION OF THE PATHWAYS OF INFECTION OF THE INTRACRANIAL STRUCTURES.

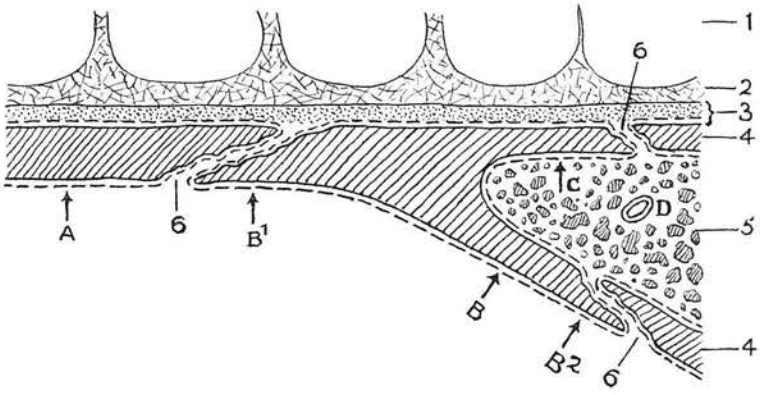


Fig.1.- 1. Brain
2. Leptomeninges
3. Dura mater
4. Compact bone
5. Red bone marrow
6. Haversian canal

To face page 14.

II. GENERAL CONSIDERATION OF THE PATHWAYS OF INFECTION OF THE INTRACRANIAL STRUCTURES.

The possible routes of intracranial infection from a primary focus outside the skull are: 1. By extension through loss of continuity in the bone; 2. by the venous blood stream; 3. by the olfactory perineural sheaths.

1. By Extension through Loss of Continuity in the Bone.- This may occur through a traumatic fracture or in certain areas through a congenital dehiscence, but takes place more frequently by erosion of the bone. This last occurs either by osteoclasts, these cells being stimulated to activity by the toxins of the bacteria causing the infection, or by the process known as halisteresis - absorption of the calcium salts through the agency of the body fluids.

The bony wall of the skull consists either entirely of compact bone or of compact bone containing red marrow (see Fig.1). When the erosion occurs through compact bone, the process may progress through the whole thickness of the bony wall (A). In an area, however, containing red marrow, the erosion may pass through the outer layer of compact bone to the diploë and so infect it (B). When the

marrow has become infected, erosion of the inner table may take place (C); but, as a rule, the infection passing from the bone marrow reaches the intracranial structures by the blood stream, i.e. by the diploic veins (D). But at any stage in the process of erosion of compact bone, a Haversian canal may be opened into (B^1 B^2), and the infection pass thence along either the blood-vessels or tissue spaces within it.

2. By the Venous Blood Stream.- Damage by toxins to the endothelial lining of a vein at the site of the peripheral focus of inflammation may cause thrombosis in the vein. The thrombus thus formed may be invaded by bacteria and become septic. The infection may extend along the vein; this vein may drain (1) into one of the larger tributaries of an intradural blood sinus, or (2) directly into the blood sinus. For instance, in the case of the cavernous blood sinus, infection of the blood spaces forming it may occur indirectly through an ophthalmic vein or directly through the small veins of the sphenoidal mucous membrane (see diagram, Fig.6). When the thrombosed peripheral vein is a Haversian vein, the infection may reach the intradural blood sinuses either directly along it or through the red bone marrow. In the osseous walls of the higher

accessory air sinuses, the diploic blood spaces drain directly or indirectly into the cavernous blood sinuses and hence the latter are readily infected.

3. By the Olfactory Perineural Sheaths.-

Mention must be made here of a persistent cranio-pharyngeal canal as a potential pathway of infection of the intracranial structures. In a certain number of cases this has been suggested as the possible route by which infection has passed to within the cranial cavity and in one case, that published by J.G. Druss and to which reference has already been made (pg.12), it is probable that this was the structure by which the infection had passed from the naso-pharynx to the substance of the sphenoid bone and thence had reached the meninges. The cranio-pharyngeal canal, or Rathke's pouch, is the invagination of the roof of the oral sinus which occurs at an early stage of embryological development and from which is formed the anterior portion of the pituitary body. In the majority of cases, obliteration of the canal occurs usually from the buccal end, begins about the end of the second month of intra-uterine life, and is complete by the end of the third month. Investigation by W. Sokaloff, A.

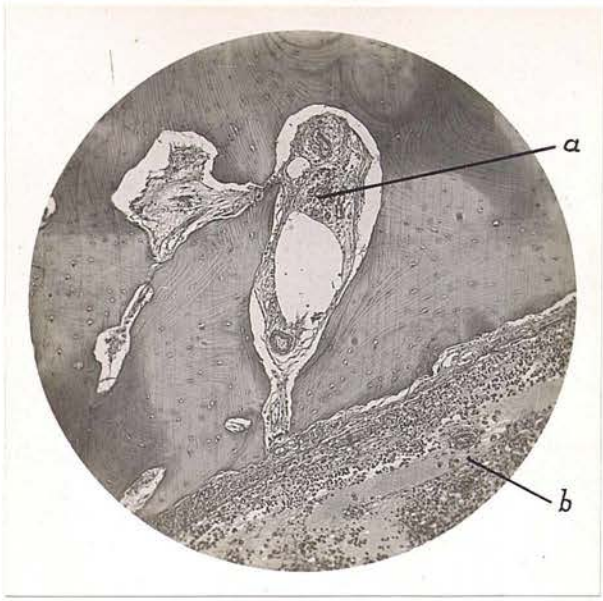


Fig.2.- The section shows a process (a) of the deeper layer of the mucosa of the sphenoidal air sinus (b) passing into the bone. The process consists of loose connective tissue with arteries, veins, and lymph spaces. (x 50 diams.)

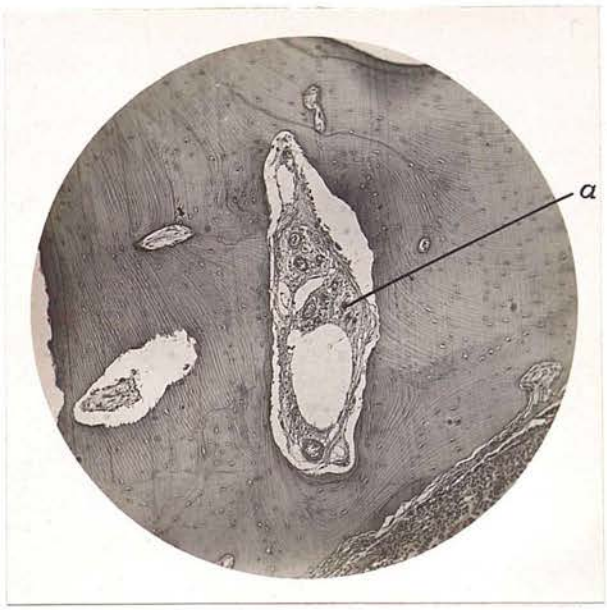


Fig.3.- The section shows the same process (a) of the deeper layer of mucosa as in Fig.2. The process is now deep in the bone. (x 50 diams.)

To face page 17.

Schultze, and others have shown, however, that the complete canal persists in from 0·3 to 0·5 per cent. of adults, and a portion of it is present in about 9 per cent. of adults.

In none of the cases comprising the present series was a persistent cranio-pharyngeal canal the pathway of infection, and when it does occur it must of necessity be a pathological rarity.

Demonstration of the Continuity of the Lymph-vascular Connections between the two Surfaces of the Cranial Bones.- The continuity of the lymph-vascular connections through the bony wall of the cranium represented diagrammatically in Fig.1 are demonstrated in the accompanying Figs. 2,3,4, and 5. The photographs were taken from a series of sections obtained from the roof of the sphenoidal air sinus of Case VII. They shew the continuity, through bone marrow, between the vessels of the deeper (periosteal) layer of the mucous membrane of the sphenoidal sinus and the outer (periosteal) layer of the over-lying dura mater. In Fig.2, a process of the deeper layer of the mucosa is seen passing into the bone. This, consisting of blood vessels with their accompanying lymph vessels and loose connective tissue, constitutes a Haversian canal. When traced in serial

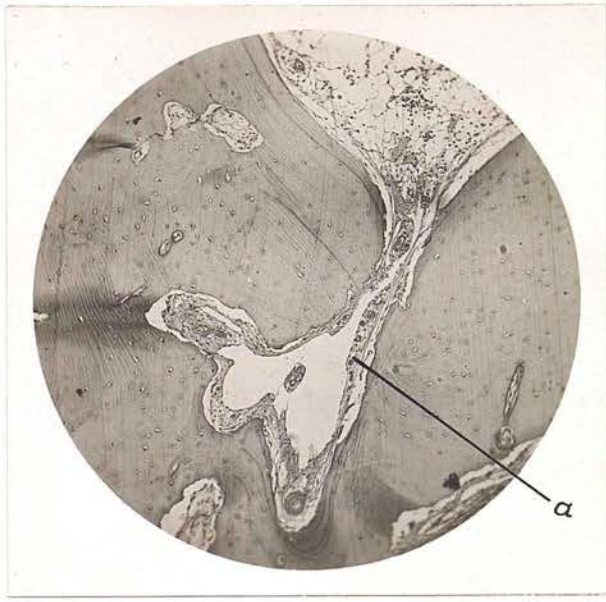


Fig.4.- The section shows the same process (a) as in Figs.2 and 3. Here it is seen to be continuous with the bone marrow. (x 50 diams.)

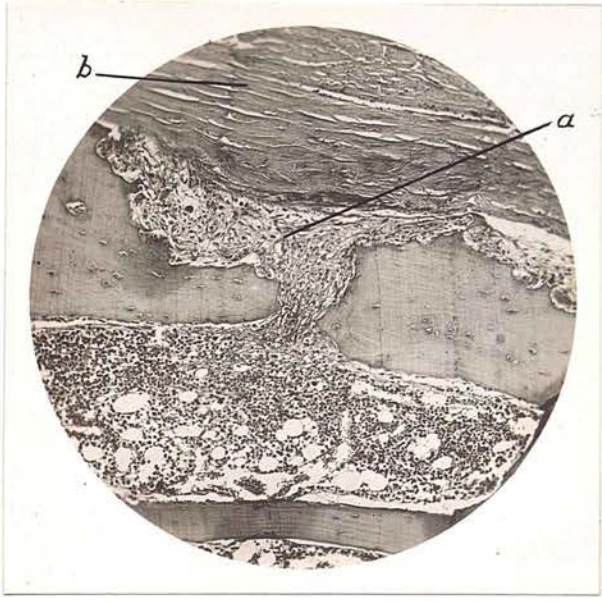


Fig.5.- The section shows a process (a) of the deeper layer of the dura mater (b) passing into the bone and becoming continuous with the bone marrow. (x 135 diams.)

To face page 18.

sections, the process was found to pass into the substance of the bone, and later became continuous with the diploe in the bony roof of the sinus (Figs.3 and 4). Further, a similar continuity of structures was shown to exist between the diploe and the outer (periosteal) layer of the dura mater (Fig.5). This arrangement between the outer and inner osseous surfaces exists in all the cranial bones.

III. SYNOPSIS OF THE CASES IN THE PRESENT SERIES.

III. SYNOPSIS OF THE CASES IN THE PRESENT SERIES.

Case No.	Designation	Primary Intracranial Condition	Nature and Site of Primary Focus	Pathway of Infection
I.	J.B.M.	Cavernous sinus thrombosis - Fulminating type	Furuncle in nose	Venous blood stream
II.	P.L.	" " "	Furuncle on upper lip	" " "
III.	W.E.	" " "	Acute inflammation of sphenoidal air sinus	" " "
IV.	D.McL.	" " "	Acute inflammation of middle ear	" " "
V.	A.B.	" " "	Chronic inflammation of middle ear	" " "
VI.	M.F.	" " "	Chronic inflammation of ethmoidal air cells	Direct extension through bone then venous blood stream
VII.	I.L.	Cavernous sinus thrombosis - Restrained type	Acute inflammation of sphenoidal air sinus	Venous blood stream
VIII.	J.K.	" " "	Chronic inflammation of middle ear	" " "
IX.	M.W.	" " "	Furuncle in nose	" " "
X.	J.W.W.	" " "	Acute inflammation of ethmoidal air cells	Direct extension through bone then venous blood stream
XI.	D.S.	" " "	" " "	" " "
XII.	J.O.B.	" " "	Acute inflammation of sphenoidal air sinus	Venous blood stream
XIII.	J.B.	" " "	Acute inflammation of middle ear	" " "

III. SYNOPSIS OF THE CASES IN THE PRESENT SERIES (Continued).

Case No.	Designation	Primary Intracranial Condition	Nature and Site of Primary Focus	Pathway of Infection
XIV.	E.A.	Acute purulent leptomeningitis	Subacute inflammation of sphenoidal air sinus	Direct extension through bone
XV.	M.R.	" " "	Chronic inflammation of ethmoidal air cells. Trauma	" " "
XVI.	A.S.	" " "	Acute inflammation of frontal air sinus	" " "
XVII.	R.P.	" " "	" " "	" " "
XVIII.	C.H.	" " "	Acute supervening on chronic nasal catarrh. Operation	" " "
XIX.	J.R.	" " "	Chronic inflammation of frontal air sinus	" " "
XX.	J.B.	Acute purulent leptomeningitis	Chronic inflammation of nasal and ethmoidal cavities. Operation	Olfactory perineural sheaths
XXI.	M.M.	" " "	" " "	" " "
XXII.	C.G.	" " "	" " "	" " "
XXIII.	A.C.M.B.	" " "	Chronic inflammation of nasal and ethmoidal cavities. No operation	" " "

IV. INFECTION OF THE INTRACRANIAL STRUCTURES BY THE VENOUS BLOOD STREAM.

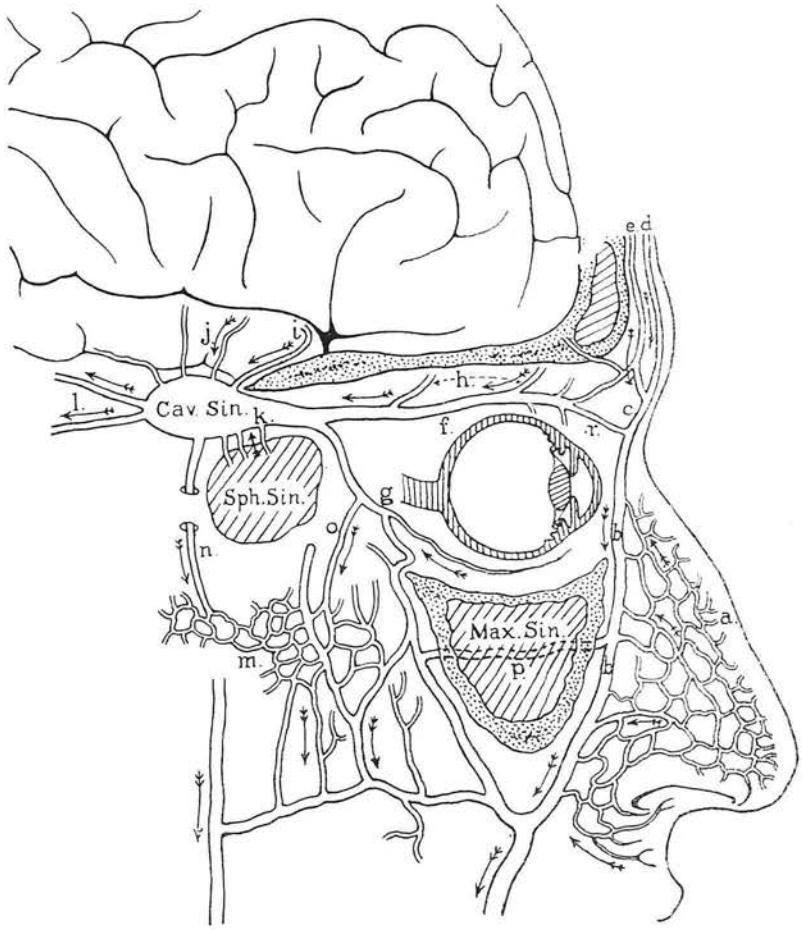


Fig.6.- Veins communicating directly or indirectly with cavernous sinus.

a. subcutaneous venous plexus.
b. ant. facial v.
c. angular v.
d. frontal v.
e. supraorbital v.
f. sup. ophthalmic v.
g. inf. ophthalmic v.
h. ant. and post. ethmoidal vs.
i. spheno-parietal sin.
j. middle cerebral vs.
k. veins from sphenoid. sin. mucosa.
l. sup. and inf. petrosal sin.
m. pterygoid venous plexus.
n. vein of Vesalius.
o. vein from inf. ophthalmic to pterygoid plexus.
p. deep facial v.
r. communicating v. between sup. ophthalmic and angular veins.

To face page 23.

IV. INFECTION OF THE INTRACRANIAL STRUCTURES BY THE VENOUS BLOOD STREAM.

The present research shews that inflammatory foci in the face, nose, and nasal accessory air sinuses causing infection of the intracranial structures by way of the blood stream, give rise, in the great majority of cases, to septic thrombosis of the cavernous blood sinus.

It is necessary, therefore, to describe briefly the anatomy and venous connections of these intradural blood spaces.

Anatomy of the Cavernous Sinus and its Tributaries.

(Fig.6)

Situated one on each side of the body of the sphenoid bone, the two sinuses communicate with each other through the intercavernous or circular sinuses. The cavernous sinus differs from the other intracranial blood sinuses in the fact that its cavity is more subdivided by fibrous strands so as to form a reticulated arrangement, the meshes of which are filled with blood.

Through a number of tributaries the cavernous sinus receives the venous blood return from a widely distributed area. Thus, through the spheno-parietal sinus it receives veins from the dura mater, and through the inferior and superficial middle cerebral veins the blood is directly returned to it from the meninges and the surface of the brain in the region of the Sylvian fissure. From the mucous membrane of the sphenoidal air cavity, the cavernous sinus receives numerous small veins transmitted through the bony wall of the air sinus.

A much wider area, however, is indirectly connected with the cavernous sinus through the medium of the ophthalmic veins and their tributaries. The supraorbital and frontal veins unite to form the angular vein, which, after a short course, is continued downwards across the face as the anterior facial vein. Through a communicating vein between the angular and the superior ophthalmic vein, the venous return from the forehead, the eyelids, the cheek and the external nose, is thus linked up with the ophthalmic system. On the margin of the orbit the superior ophthalmic receives an additional tributary from the frontal diploe, and, within the orbit, branches from the anterior and posterior ethmoidal air sinuses (veins of the same name) and small

branches (ciliary veins) from the tissues of the orbit itself.

Lastly, it must be remembered that in the subcutaneous tissue of the nose, as elsewhere, there is a considerable and very freely communicating network of small capillary blood vessels, which connect together the relatively larger veins in the region.

The inferior ophthalmic vein, having effected a communication with the pterygoid venous plexus through the inferior orbital fissure, terminates like the superior ophthalmic in the anterior part of the cavernous sinus. This union takes place either directly or through a trunk common to it and the superior ophthalmic vein. When infection reaches the cavernous sinus from the various areas just enumerated, it is carried for the most part in the direction of the returning blood stream.

On the other hand, blood is transmitted from the cavernous sinus to the pterygoid venous plexus situated outside the skull in the infratemporal fossa. This is effected through a few small veins which traverse the foramen ovale or the canal of Vesalius. Through this connection the cavernous sinus is brought indirectly into venous relation with the soft palate, the fauces, the pharynx and the alveolar processes of the upper and lower jaws, as

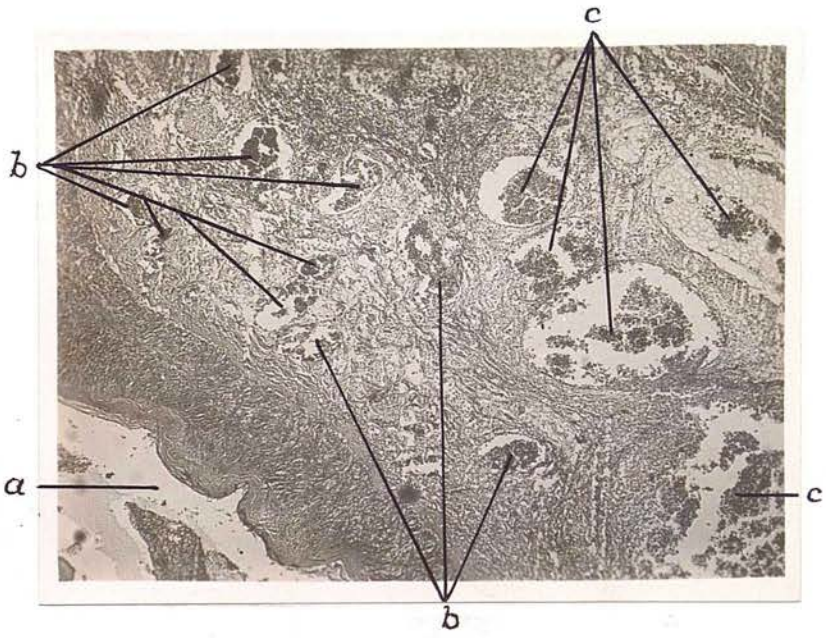


Fig.7.- Microphotograph of a portion of a section cut in the coronal plane through the middle of the pituitary body. The illustration shows some of the small veins which form the carotid venous plexus.

a. Lumen of carotid artery.

b. Veins of carotid venous plexus.

c. Blood spaces of cavernous sinus.

To face page 25.a.

the veins from these areas enter the pharyngeal and pterygoid plexuses, which communicate with each other. In the event of septic thrombosis occurring in the pterygoid plexus from a primary focus in one of these areas, the cavernous sinus may become secondarily infected by a process of retrograde thrombosis or embolism.

In order to complete the anatomical picture, reference must be made to the posterior communications of the cavernous sinus with the lateral blood sinus and the jugular bulb, through the superior and inferior petrosal blood sinuses. Through these channels a septic focus in the middle-ear cleft or labyrinth may give rise to a retrograde septic thrombosis of the cavernous blood sinus. Further, the lateral blood sinus, through the medium of the mastoid emissary vein, effects a communication with the superficial veins in the retro-auricular region. Lastly, as the internal carotid artery passes through its canal in the base of the skull and through the more posterior part of the cavernous blood sinus, it is surrounded by a plexus of small veins - the carotid venous plexus (Fig.7). The plexus communicates above with the anterior part of the cavernous sinus and below with the internal jugular vein or with the pharyngeal plexus of veins

(Cunningham and Robinson). It receives small tributaries which in part drain the tympanic cavity and thus the carotid venous plexus forms a second route by which the middle ear is in venous relationship with the cavernous blood sinus.

After this brief anatomical description, the possible modes of infection of the cavernous blood sinus may now be considered.

When acute bacterial inflammation is present around a small blood vessel (capillary or venule) transfusion of the bacterial toxins and of the products of tissue autolysis through the vessel wall may cause injury to the endothelial lining. The damage is manifest by the endothelial cells becoming swollen, and on these cells blood-clot is deposited. The thrombus at the primary site, at first aseptic, may become infected later by bacteria.

This process is well exemplified in Case II, that of a girl who developed a septic focus on the mucosal surface of the upper lip which led to her death from cavernous sinus thrombosis and pyaemia (Figs.32 and 33).

The clot thus formed may extend along the blood vessel and thence into the larger vein of which it is a tributary, the process being exactly similar, namely, progressive damage to the endothelium with

an advancing aseptic clot and subsequent infection by the micro-organisms. The micro-organisms may be localised to foci in the clot, or may be distributed generally throughout it.

Again, it is possible that the bacterium itself may obtain access to the lumen of the blood vessel; if not destroyed by the blood, it will tend to form a colony which, acting as a foreign body, provides a nucleus around which clotting takes place. This hypothetical mode of origin of the thrombus has not been demonstrated, however, in any of the present series of cases, and it is self evident that the histological proof of such an origin for the thrombus would be a matter of chance.

The further extension of the infective process into the cavernous blood sinus, giving rise to a septic thrombosis there, may be by one of several methods, namely:-

(a) By septic thrombosis of veins:

(1) Direct extension along tributary veins;

(2) Retrograde embolus of a portion of a septic thrombus.

(b) Without thrombosis of veins:

(1) Along the subcutaneous venous plexus;

(2) Along perivascular lymph spaces and then by the venous blood stream;

(3) As retrograde emboli;

(4) By selective action.

These methods are discussed in detail in relation to Case I (pg.49).

As elsewhere in the venous system, thrombosis in the cavernous sinus begins around a localised focus of damaged endothelium. The clot extends from this nidus and eventually the whole of the blood spaces of the sinus are filled completely with thrombus. Nor does the thrombotic process stop here; it extends along any or all the tributaries and connections of the cavernous blood sinus, and hence not only is the opposite sinus involved, but by direct extension a septic clot is formed in parts of the body distant considerably from the sinus itself. In many instances this spreading thrombosis extends along the veins in a direction retrograde to the normal blood stream.

In cases in which thrombosis of the cavernous blood sinus has occurred some time before death, it will be understood from the above that it is quite impossible to distinguish which of the many tributary thrombosed veins was the one primarily involved and by which the thrombotic process extended from the primary focus of infection to the cavernous blood sinus. In every case the manner and the actual path of primary extension must be a matter of opinion

based on clinical, macroscopic, and microscopic evidence.

Thrombosis, therefore, may be of three main types:-

1. The purely aseptic thrombus, in which the clot is aseptic throughout the whole process: This is seen in marasmus and in primary anaemias; but in these conditions it must be borne in mind that the clot is induced probably by an altered condition of the blood itself, and not as the result of pathological changes in the vessel walls.

2. The infected thrombus, in which the infection is restrained but not controlled: Cases XI and XII are examples of this type: Cases of recovery from septic thrombosis of the cavernous sinus belong to this group, e.g. Case XIII.

3. The fulminating type, in which the infection is not restrained: Clotting occurs rapidly, the thrombus becomes infected almost as soon as formed, breaks down and gives rise to general pyaemia. This type is exemplified by the cases of cavernous sinus thrombosis commonly met with.

All degrees of sepsis occur between the purely

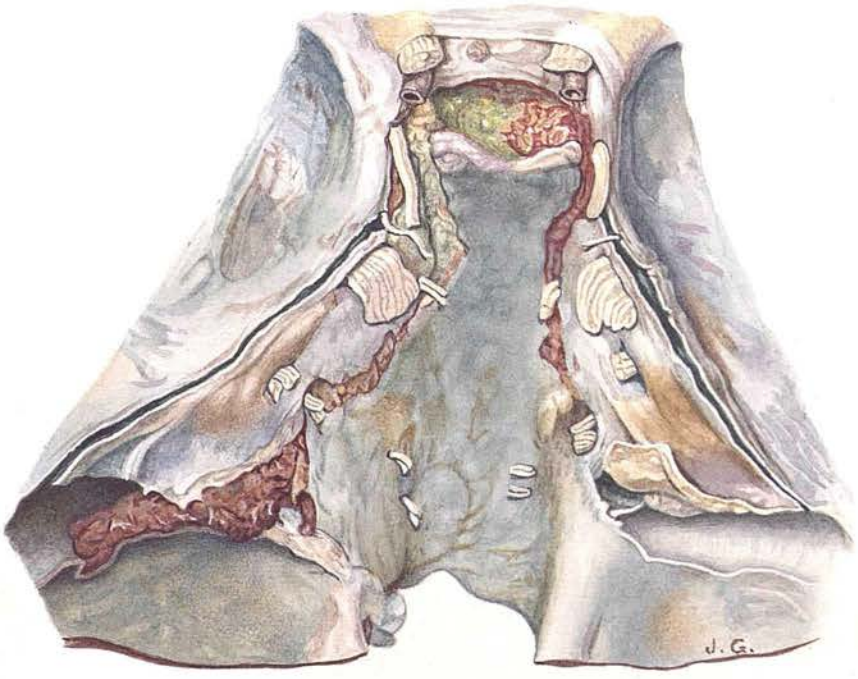


Fig.7a.- Drawing of a specimen kindly lent to the author by Dr A.Logan Turner to illustrate progressive thrombosis secondary to that of the cavernous blood sinuses. The illustration shows the base of the middle cranial fossa from a case of bilateral sphenoidal air sinus suppuration with cavernous sinus thrombosis. Pus is present in both cavernous sinuses. On the left side it has extended some distance into the inferior petrosal sinus; the remaining portion of the sinus to its entrance into the jugular bulb is clotted and from here the clot extends upwards along the sigmoid part of transverse (lateral) sinus for about 2 cm.. On the right side, a thrombus extends from the cavernous sinus throughout the greater part of the inferior petrosal sinus, but has not yet reached the jugular bulb. Except for a small clot at its origin, the left superior petrosal sinus is empty as is the whole of the right. Pus is present beneath the pituitary body and there is a basal meningitis. (Case of A.H., died March, 1922).

To face page 30.

aseptic thrombosis and the fulminating type.

That a progressive thrombosis of tributary veins occurs secondary to thrombosis of the blood sinus is a fact upon which too much insistence can not be laid, and in each case, when considering the particular venous pathway by which infection has reached the intracranial blood sinus, this phenomenon must always be kept clearly in mind. The writer submits that failure to grasp the pathological importance of the occurrence of a progressive thrombosis of veins, secondary to thrombosis of the blood sinus of which they are tributaries, has caused, in many instances, wrong deductions to be drawn from histological data.

Some authors including Sir William Macewen, H. Brunner and F. Miodowski mention cavernous sinus thrombosis occurring secondarily to acute purulent leptomeningitis. In purulent leptomeningitis it is a common occurrence for the superficial cerebral arteries and veins running in the pia-arachnoid spaces to be bathed in pus. It might be presumed, therefore, that the formation of a septic clot in the veins would frequently result, and that by extension of the thrombotic process within the lumen, the dural blood sinuses would ultimately be the site

of septic thrombosis.

As a matter of actual observation, however, in no case of undoubted primary leptomeningitis, for example acute purulent leptomeningitis of otitic origin, has the writer ever seen a septic thrombus in a pial vein, and this statement is made from an experience extending over many years and from the examination of numerous microscopical sections taken from many such cases.

It is suggested that the explanation of the discrepancy between the deduction that thrombosis of pial veins would be frequent and the actual observed phenomenon that this is not the case, lies in the fact that the blood vessels passing through the leptomeninges are for the most part large in size and that consequently their walls are relatively thick. The great bulk of the blood carried by the arteries in the pia mater is for the nourishment of the component tissues of the brain - nervous parenchyma and interstitial - and the venous drain is from these tissues. The capillaries which constitute the link between the arterial and venous sides of the cerebral circulation lie in the brain itself, at some distance, therefore, from the pia-arachnoid membrane and in a situation to which the pus usually does not penetrate. The smaller the blood vessel, the less is the outer

covering to its endothelium and the more liable is the latter to be damaged by diffusing toxins. For this reason the endothelium of the capillaries and smaller venules is more liable to injury by toxins from a neighbouring septic focus than is the endothelium of other parts of the circulatory system.

Certainly, in the deeper layers of the pia mater, arterioles leave the arteries to penetrate the superficial portion of the cerebral cortex and corresponding venules emerge from the cortex to enter the veins in the pia mater, but their course in the latter membrane is short and consequently the danger of damage from pus in the pia-arachnoid spaces is minimised.

Again, very few capillaries are present in the leptomeninges; the reason for this can be readily understood since, owing to the nature of the component elements of the leptomeninges, the nourishment required from the blood plasma is small. The great majority of the blood vessels in the pia-arachnoid are larger than capillaries and, under physiological conditions, they are designed for the transmission of blood and not for the transudation of plasma. This is shewn by the fact that the lumbar cerebrospinal fluid normally contains only a mere trace of albumen (15 to 45 mg. per 100 c.c.) and some of it is derived

probably from the choroid plexus since the ventricular fluid has an albumen content of 5 to 15 mg. per 100 c.c. (Ayre and Solomon quoted by Levinson).

Lastly, as will be shown in the fatal cases in the present series, in every instance in which septic thrombosis of the cavernous blood sinus was the primary intracranial complication, purulent leptomeningitis occurred secondarily.

In view of the above facts, the writer is of the opinion that when septic thrombosis of the cavernous sinus and purulent leptomeningitis occur in the same case, unless they have arisen independently of each other as in Case XIV of the present series, the purulent inflammation of the leptomeninges is secondary to the thrombosis of the cavernous sinus and is not the primary intracranial complication.

A certain number of cases have been published in which suppuration in the nasal accessory sinuses has given rise to a fatal purulent leptomeningitis and in which no disease of the cranial bones could be detected by the naked eye either at operation or at autopsy. In some of these cases, the authors have concluded that the infection has passed to the leptomeninges by the blood stream.

Attention has been drawn (pg.5 et seq) to the few cases of this nature in which microscopical investigations have been made and in which thrombosed osseous or diploic veins have been demonstrated. Further, reasons have been given why the writer is unable to accept the evidence put forward as being sufficient to substantiate the claim that in these cases the acute leptomeningitis had arisen as a primary intracranial lesion due to thrombosis of the osseous or diploic veins. Further, it must be remembered that the development of the classical signs of cavernous sinus thrombosis is due to several factors of which the rate of formation and the completeness of the thrombus in the blood sinus are of especial importance. It is understood that in the absence of these classical signs, a clinical diagnosis of cavernous sinus thrombosis is extremely difficult and in most cases impossible. This means that when the signs are absent, cavernous sinus thrombosis is unsuspected during life, and in some of the published cases now being considered, no mention is made of the examination of the cavernous sinus at autopsy. It may be concluded, therefore, that this was not carried out.

Again, experience has taught the writer that a certain number of cases occur in which a thrombus in

the cavernous sinus can be established only by microscopical examination, e.g. Case VII.

Although no case of leptomeningitis arising as a primary intracranial complication due to infection of the venous system has been met with in the present series, the possibility of its occurrence must be considered.

Firstly, near the site of the dural blood sinuses a certain number of comparatively small veins leave the deeper layers of the pia mater and crossing outwards through the pia-arachnoid spaces enter the dura mater; in this structure they pass to the dural blood sinuses into which they empty their blood.

Secondly, the perforating osseous veins enter the dura mater and, pursuing a longer or shorter course in this membrane, terminate either by opening directly into the dural blood sinuses, or by joining other veins in the dura mater form common trunks which open into the blood sinuses.

Thirdly, the veins of the dura mater itself, although few in number, terminate in the same way as do the perforating osseous veins.

Throughout the body, small veins anastomose freely and in the dura mater, the small veins from the pia mater, the perforating osseous veins, and

the dural veins effect a liberal communication with each other.

It follows, therefore, that a septic thrombus, derived from the peripheral focus of inflammation and spreading along a perforating osseous vein, can extend into its dural portion; thence it may be continued directly into the small veins from the pia mater and through them give rise to purulent leptomeningitis.

Hence on anatomical and pathological grounds, it is possible for a purulent leptomeningitis to occur as a primary intracranial complication in infection of the venous blood stream from a peripheral focus of inflammation. For reasons already given (pg.8), in the writer's opinion, in none of the cases referred to has it been proved that the leptomeningitis had actually arisen in this manner.

The cases of the present series in which cavernous sinus thrombosis was the primary intracranial complication may be grouped according to the anatomical situation of the extracranial focus of infection in relation to the cavernous sinus. In such an arrangement the cases fall into three groups as follows:-

Group 1. Cases in which the peripheral focus was situated in front - Cases I, II, and IX. To

this group belongs a sub-group in which the progress of the infection began by direct extension through bone and then reached the cavernous sinus by the venous blood stream - Cases VI, X, and XI.

Group 2. Cases in which the peripheral focus was situated below and medially - Cases III, VII, and XII.

Group 3. Cases in which the peripheral focus was situated posteriorly - Cases IV, V, VIII, and XIII.

A grouping of the cases on this basis, however, does not arrange them in pathological sequence; each of the above three groups contains cases in which the cavernous sinus infection pursued a fulminating course, death occurring within one week of the infection of the blood sinus, and cases in which the infection of the cavernous sinus followed a slower course, death not occurring until more than one week after the thrombosis, and in one case (Case XIII) in which recovery took place.

From the pathological standpoint, therefore, it is better to adopt the classification indicated on page 29 and to divide the cases into those which are fulminating in type (Cases I to VI inclusive) and those in which the infection was restrained (Cases VII to XIII inclusive).

CASES IN WHICH THE INFECTION OF THE CAVERNOUS BLOOD SINUS WAS NOT RESTRAINED (FULMINATING TYPE)

CASES I. to VI. INCLUSIVE.

Case 1.

Fig.8.

Fig.9.

Fig.8.- The illustration shows the patient on admission, on 18th June.

Fig.9.- The patient on 19th June, the last day of his illness.

To face page. 39.

CASE I. Furuncle of Right Nasal Vestibule: Septic Thrombosis of the Cavernous Blood Sinuses: Leptomeningitis: Death: Autopsy.

J.B.M., male, aged 31, was a patient in Morningside Asylum, Edinburgh. On the 13th June, 1924, a small boil formed on the inner aspect of the ala of the right nasal vestibule, and the skin on the external surface of the nostril became swollen. On the evening of the 15th June, forty-eight hours later, the abscess burst and there was a free discharge of pus. The external swelling decreased in size, the temperature, previously elevated, fell to normal and the patient was more comfortable. There was no history of pre-existing nasal discharge.

On the 16th June, the patient complained of headache and the temperature was 99°F. On the morning of the 17th, he vomited a quantity of greenish-coloured fluid. Headache was now less severe, but the temperature remained at 99°F. and the pulse was 80. During the afternoon of the same day he again vomited.

On the morning of the 18th June, the condition was distinctly worse; both eyeballs were observed to be prominent and the patient complained of

dimness of vision. His mental condition was not affected. During the same day he was transferred to the Royal Infirmary, where he was seen by Mr J. N.J. Hartley, F.R.C.S.Ed., to whom I am indebted for the photograph which illustrates the patient's condition just before admission to the hospital (Fig.8).

Both upper eyelids were oedematous; chemosis of the ocular conjunctiva was observed in each eye, and both eyeballs were proptosed. A granulation inside the right nostril indicated the site of the boil. The thermometer registered 102·6°F. and the pulse was 108. The patient was conscious and answered questions intelligently. He was admitted to the Ear and Throat Department under the care of Dr W.T. Gardiner, to whom I am indebted for the photograph (Fig.9) illustrating the patient's appearance on the morning following his admission.

During the night he became worse and, on the morning of the 19th June, the conjunctival chemosis had become aggravated and both eyeballs were immobile. The temperature rose to 106°F.; the patient rapidly became unconscious and died in the course of the day. It is unfortunate that no ophthalmoscopic examination was made. The duration of the illness was six to seven days.

Autopsy.- At the request of the relatives, examination was limited to the head. It was not permissible to remove the veins of the face. The oedema of the eyelids and bilateral proptosis were still present when the body was placed on the post-mortem table. A diffuse, purulent leptomeningitis extended over the under surface of the brain, including the orbital surface of the frontal and inferior aspect of the temporal lobes. The middle-ear clefts and the frontal and maxillary sinuses were normal.

Preparation of Material for Microscopic Examination.- A large block was removed from the base of the skull; on each side the incisions were made in the sagittal plane passing lateral to the orbit and through the middle fossa of the skull. The anterior face of the block was cut in the coronal plane through the nasal cavities and both orbits, and the posterior face in the same plane through the basisphenoid.

The whole block was decalcified for several months in Parenny's solution. The redundant tissue was then removed with a knife, and the remaining portion was subdivided in the coronal plane into pieces suitable for embedding in paraffin. The

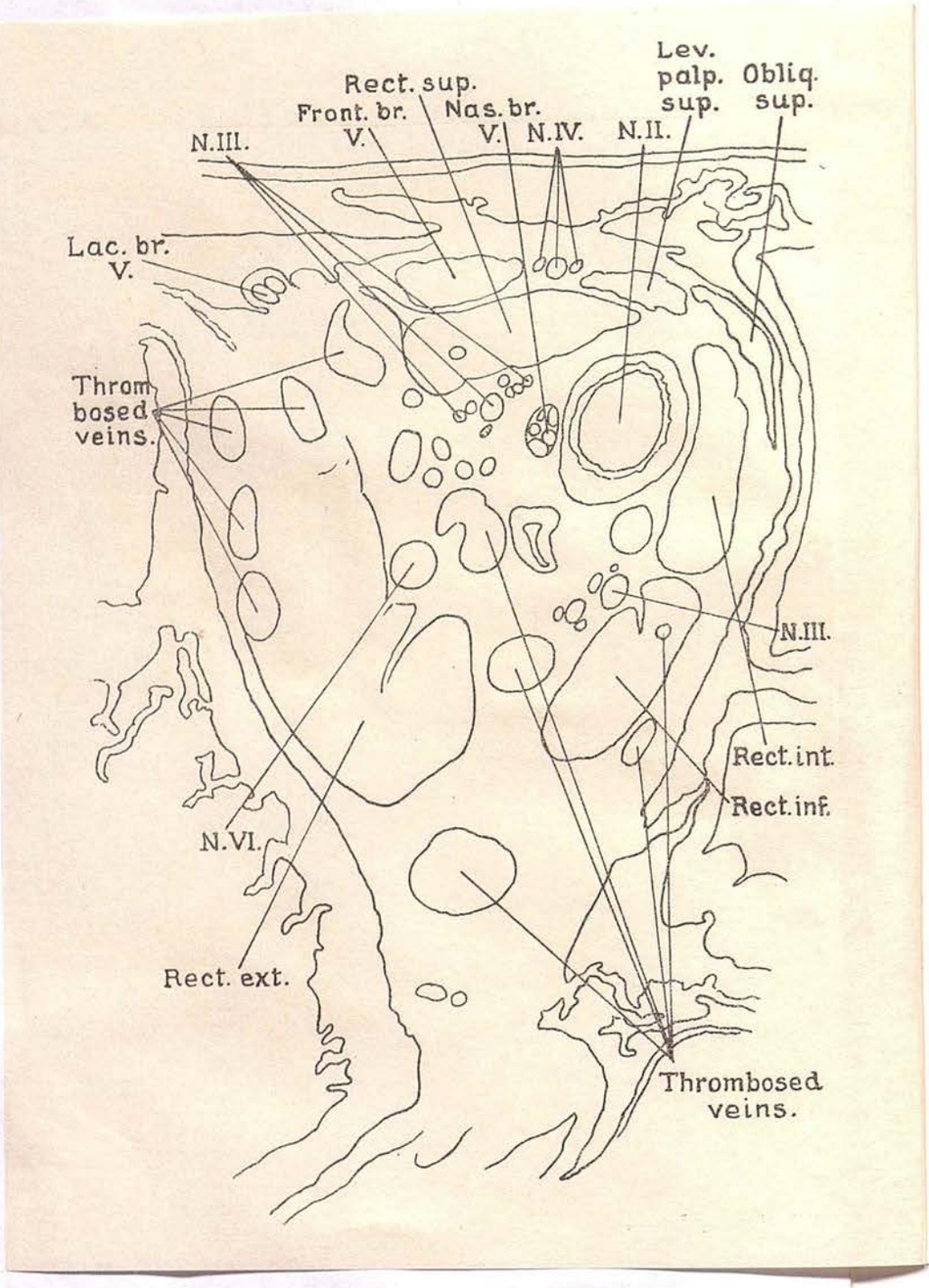


Fig.10.- Coronal section (viewed from the front) through the right orbit immediately posterior to the plane of the ciliary ganglion. (Stained by Mallory's method.)

To face page 42.

majority of the sections were stained by Mallory's method.

Report on the Material Examined Microscopically.

Series 1. (The Right Orbit and Surrounding Structures).- A series of 1130 sections was made in the coronal plane from before backwards, every tenth section being mounted and stained. The anterior sections commenced immediately behind the ciliary ganglion and demonstrated the right orbital contents, the neighbouring posterior ethmoidal air cells, and the mucosa covering the upper part of both nasal cavities (Fig.11). The posterior sections in the series comprised the structures at the apex of the orbit and in the sphenoidal fissure along with the anterior portion of the right cavernous blood sinus.

In the most anterior of the sections, all the veins in the orbit, with the exception of three, were filled with septic thrombi (Figs,10 and 12), and, in many instances, the walls of the veins were necrosed and pus had escaped into the surrounding fatty or muscular tissue. The three small veins which did not contain septic thrombi were situated about the centre of the field (Fig.10); on tracing these further back, however, septic thrombosis was found to have occurred in them.

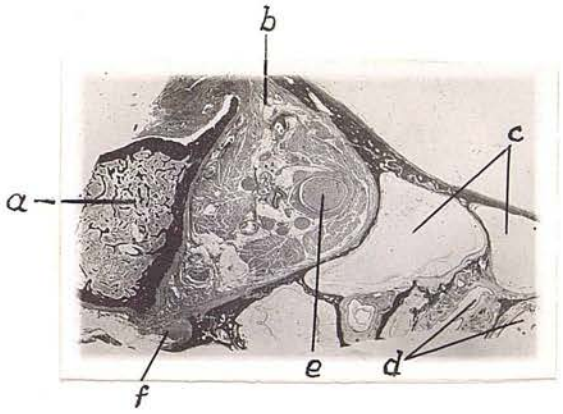


Fig.11.- R. orbit and adjacent post. ethm. cells.

a. Great wing sphen. b. Sup. orb. fiss.
c. Post. ethm. cells. d. Nas. fossae.
e. N.II. f. Inf. orb. fiss.

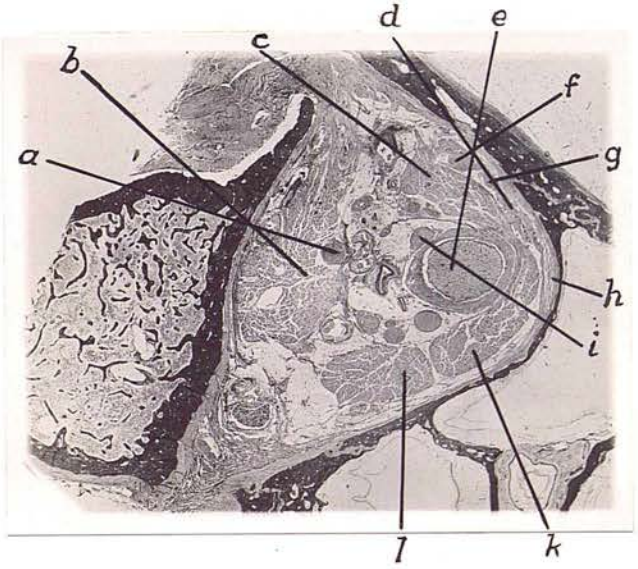


Fig.12.- R. orbit showing veins with septic thrombi.

a. N.VI. b. Rect. ext. c. Rect. sup.
d. Lev. palp. sup. e. N.II.
f. Front. br. N.V. g. N.IV.
h. Obliq. sup. i. Nas. br. N.V.
k. Rect. int. l. Rect. inf.

To face page 43.

In the sections made from the more posterior part of the orbit, some of the veins in the lower part of the orbital cavity were seen to have united to constitute the inferior ophthalmic vein, while others in the upper part had formed the superior ophthalmic vein. The two ophthalmic veins terminated in a short common trunk, which opened into the anterior part of the cavernous blood sinus. Throughout their entire course the ophthalmic veins contained septic thrombi (Figs.13, 14), the clot being continuous, on the one hand, with that found in the small veins of the orbital cavity, and, on the other hand, with the septic clot filling the cavernous blood sinus.

Further, the sections showed also the right spheno-parietal blood sinus lying on the under surface of the lesser sphenoidal wing; it contained a septic thrombus (Fig.15).

Examination of the mucosa of the posterior ethmoidal air sinus adjacent to the orbit revealed septic thrombosis of some of the smaller veins in its deeper (periosteal) layer (Fig.16). These veins were continuous with a small vein entering a Haversian canal in the lateral bony wall of the air sinus (medial bony wall of the sphenoidal fissure). This Haversian vein passed through the compact bone

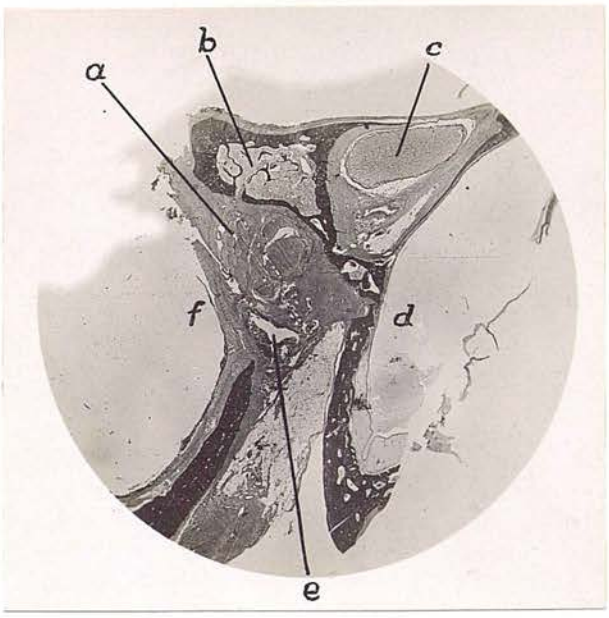


Fig.13.- R. common ophthalmic venous trunk with septic thrombus.

a. Nerves. b. Small wing sphen. c. N.II. d. Post. ethm. cells. e. Common ophth. trunk. f. Mid cran. foss.

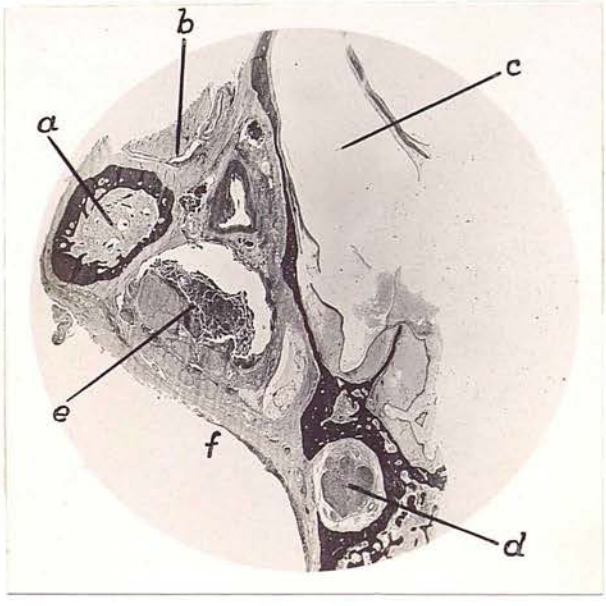


Fig.14.- R. common ophthalmic venous trunk with septic thrombus.

a. Ant. clin. proc. b. N.II. c. Post. ethm. cell. d. Max. div. N.V. e. Common ophth. trunk. f. Mid. cran. foss.

To face page 44.

into the red marrow. The latter showed extensive septic inflammation. From the red marrow again, another small vein containing a septic thrombus was traced laterally through a Haversian canal in the compact bone into the cavernous blood sinus (Fig.17).

Further, small veins in the dura mater covering the cerebral wall of the great wing of the sphenoid bone in the middle fossa of the skull were filled with septic thrombi (Fig.18); the thrombosis extended along these veins into the thrombosed cavernous blood sinus.

Series 2 (The Left Orbit).- The sections in this series comprised the tissues of the left orbital cavity and its bony walls. Like those in Series 1, they were cut from before backwards, but commenced on a more anterior plane, as the earlier sections showed the ciliary ganglion. The changes observed were the same as on the right side, namely, septic thrombosis of all the larger and smaller veins of the orbital cavity, with extension of the pus from their lumina into the surrounding tissue (Fig. 19). As the preliminary sections showed pathological conditions similar to those seen in the right orbit, a complete series was not prepared.

Series 3 (Sphenoidal Air Sinuses and Cavernous Blood Sinuses).- This series was cut from before

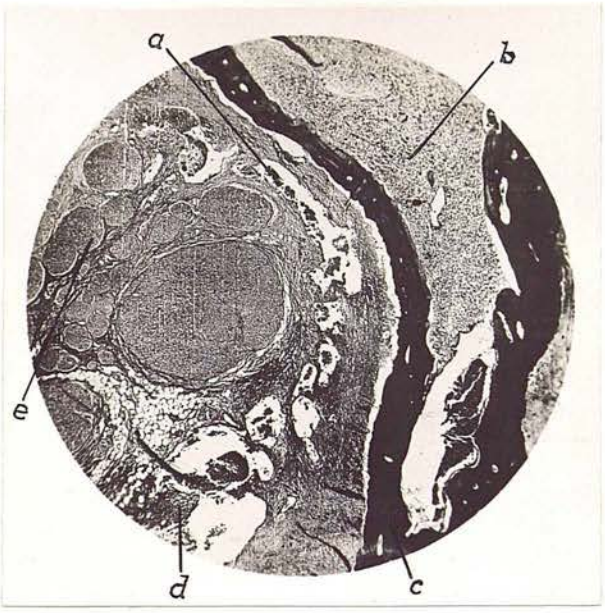


Fig.15.- R. spheno-parietal blood sinus with septic thrombus.

a. Spheno-par. sin. b. Diploe ant. clin. proc. c. Bone. d. Ophth. vein. e. Nerve bundles.

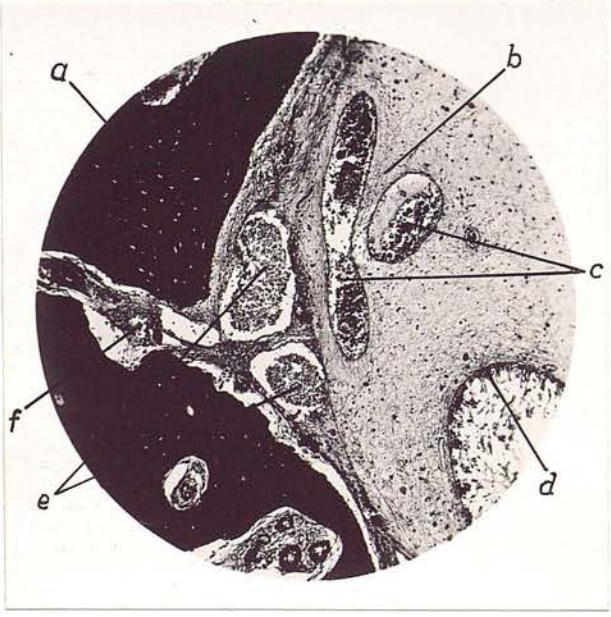


Fig.16.- Lateral wall of r. post. ethm. air cell with septic thrombus in small veins of deep (periosteal) layer of mucosa; the septic thrombus extends into the vein of a Haversian canal.

a. Bone. b. Muc. memb. c. Non-thrombosed veins. d. Ciliated epithelium. e. Thrombosed periost. veins. f. Septic thrombus in Haversian vein.

To face page 45.

backwards in the coronal plane, through the anterior lobe of the pituitary. The sections demonstrated both sphenoidal air sinuses and their walls, the two cavernous blood sinuses and the circular sinus (Fig. 20). In this patient, the right sphenoidal cavity was small and limited to the anterior part of the body of the sphenoid. The left sphenoidal cavity, on the other hand, extended across the mesial plane, occupying posteriorly the whole transverse diameter of the body of the sphenoid.

The cavernous blood spaces were filled completely by septic clot,(Figs.21,22), the whole clot, as in the rest of the affected veins seen in all the sections in this case, being densely infiltrated with polymorphonuclear leucocytes. The diploë in the bony wall of both air sinuses showed marked septic inflammation, actual pus being present in those portions in which the red marrow was large in amount, e.g. in the inferior wall. In the bony floor of the large left sphenoidal air sinus, veins of moderate size were seen filled with septic thrombi, and in the immediate neighbourhood the mucosa of the air sinus was stripped from the bone by a collection of pus (Fig.23). The vein accompanying the left Vidian nerve was observed lying in a canal in the osseous wall of the floor of the left sphenoidal air sinus.

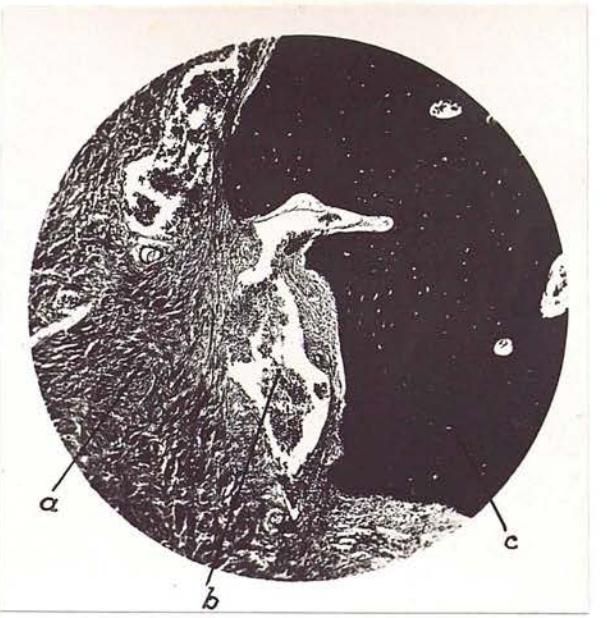


Fig.17.- Cranial aspect of lateral wall of r. post. ethm. cell as in Fig.8. The vein with septic thrombus leaves cranial aspect of bony wall of post. ethm. cell and was traced to the infected r. cav.sin.

a. Dura mater. b. Vein with septic thrombus. c. Lateral bony wall of ethmoid cell.

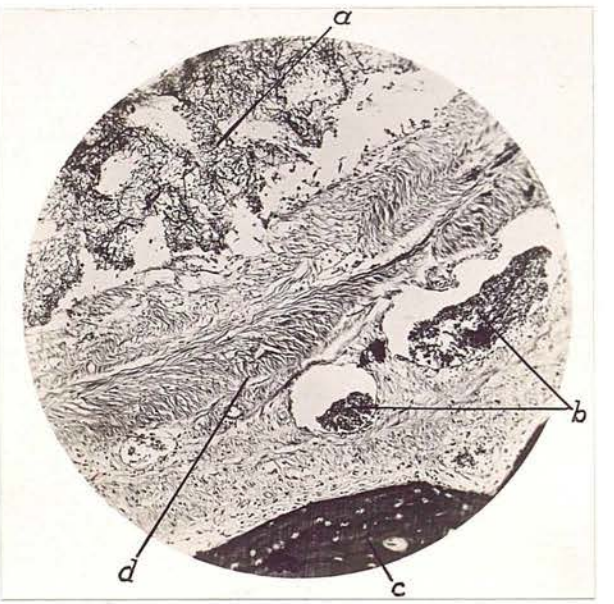


Fig.18.- Meninges of mid. cran. foss. at apex of r. orbit. Veins of dura mater contain septic thrombi; pus infiltrates pia-arachnoid meshes.

a. Pia-arachnoid. b. Septic thrombi in veins of dura mater. c. Great wing sphenoid. d. Dura mater.

To face page 46.

This vein was filled with septic clot, the pus escaping from it into the fatty tissue in the small canal (Fig.20).

Series 4 (Left Sphenoidal Air Sinus and both Cavernous and Circular Blood Sinuses).- This series was also cut from before backwards in the coronal plane through the posterior portion of the pituitary. The sections, like those in Series 3, showed complete thrombosis of the cavernous and circular blood sinuses and extensive inflammation of the diploë of the bony walls of the left sphenoidal air sinus.

Series 5.- The sections were made from a block removed from the body of the sphenoid bone below the floor of the air sinuses. The bone showed extensive septic inflammation, with formation of pus in the diploë (Fig.25).

The Mucous Membrane of the Nasal, Ethmoidal and Sphenoidal Air Cavities.- (a) No pathological changes were observed in the mucosa covering the ethmoidal area of both nasal cavities (Fig.24). The columnar lining cells were intact and the glands in the substance of the mucosa were not unduly active.

(b) The mucous membrane of the right ethmoidal cells showed little alteration from the normal. In some places there was a certain amount of oedema with diffuse infiltration by cells, mostly of the large,

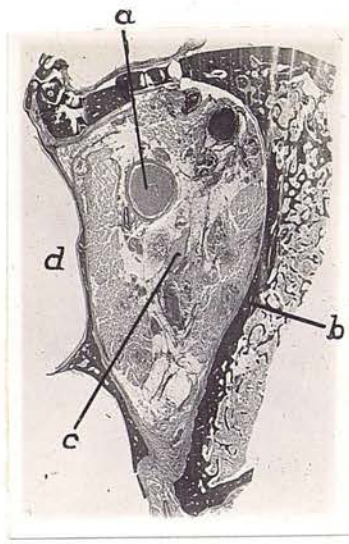


Fig.19.- L. orbit showing changes similar to those in the r. orbit.

a. N.II. b. Great wing sphenoid. c. Ciliary ganglion. d. Post. ethm. cell.

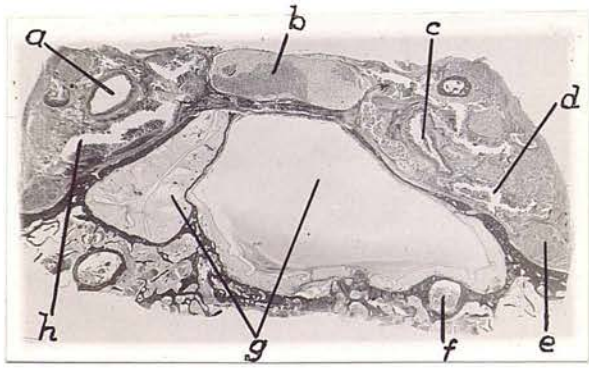


Fig.20.- General topography of the cavernous blood sinuses.

a. R. int. carotid art. b. Pituitary. c. L. int. carotid art. d. L. cavern. sin. e. Max. div. N.V. f. L. Vidian canal. g. R. and L. sphen. sin. h. R. cavern. sin.

To face page 47.

mononucleated type.

(c) The mucosa lining the floor of both sphenoidal air sinuses (Fig.20) was oedematous, the blood vessels were dilated and there was some diffuse infiltration by polymorphonuclear and large mononucleated cells. In the neighbourhood of the abscess already described as situated between the deep periosteal layer of the mucosa and the bone (vide Series 3, pg.45), the signs of acute inflammation were more pronounced and a small haemorrhage was present in the substance of the mucosa (Fig.23). Early inflammatory changes were inconspicuous or absent in the mucous membrane covering the upper part of the lateral walls and on the roof of the sphenoidal air sinuses. The cavities of both air sinuses contained mucous secretion.

The Diploë or Red Marrow.- In the various sections in which the diploë was demonstrated, extensive septic inflammation existed. The red marrow showing this change formed part of the outer wall of the two orbits (great wings of sphenoid), the lesser wing of the sphenoid, including the right anterior clinoid process, and the bony floor of both sphenoidal air sinuses. Many of the veins in the diploë contained septic thrombi (Figs.26, 27) and in numerous instances the thin venous walls had broken down,

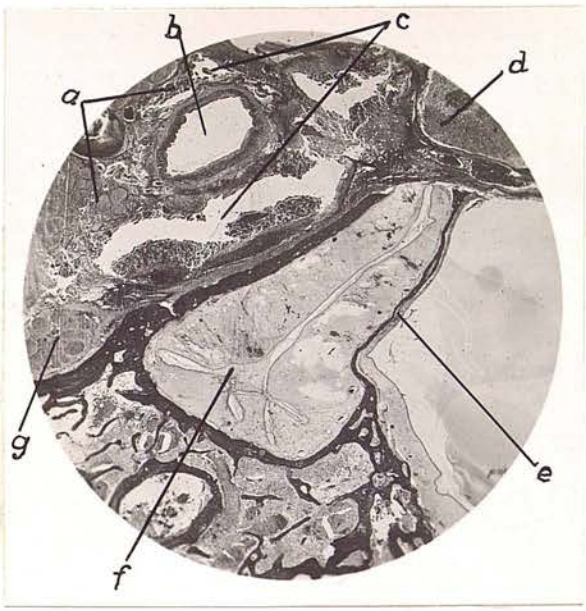


Fig.21.- Septic thrombosis of the r. cavernous blood sinus.

a. Nerve bundles. b. Int. carotid art. c. Cavern. sin. d. Pituitary. e. Intersin. septum. f. R. sphen. sin. g. Max. div. N.V.

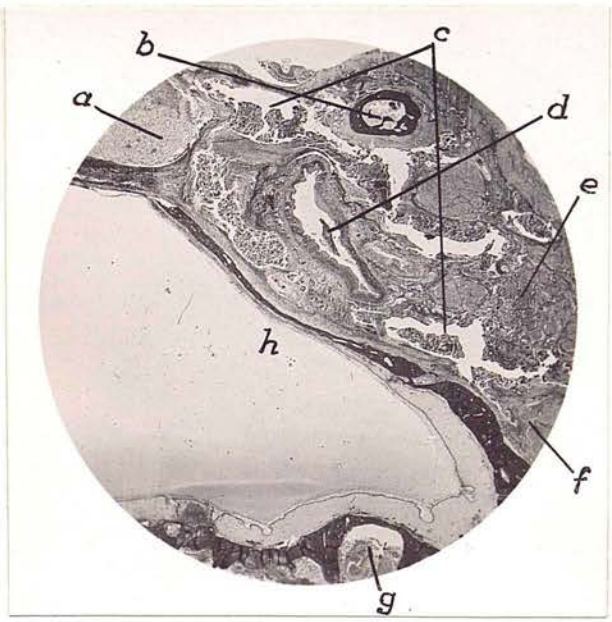


Fig.22.- Septic thrombosis of the l. cavernous blood sinus.

a. Pituitary. b. Ant. clin. proc. c. Cavern. sin. d. Int. carotid art. e. Nerve bundles. f. Max. div. N.V. g. L. Vidian canal. h. L. sphen. sin.

To face page 48.

the pus escaping into the surrounding bone marrow.

Brain and Leptomeninges.- The brain along with the leptomeninges was removed at autopsy and the whole fixed in formalin solution. After fisation, the brain was examined macroscopically by means of sections cut in the coronal plane. A section made 0·75 cm. anterior to the optic chiasma revealed a red area 1 cm. in diameter, situated in the portion of the right frontal lobe contiguous to the temporal lobe on the one hand and the caudate nucleus on the other (Fig.28). Microscopic sections of the reddened area showed it to be an early abscess. The brain tissue was necrosed and infiltrated with cells, many of which were polymorphonuclear leucocytes. Liquefaction was just commencing in the centre.

The abscess was situated very near the pia mater of the Sylvian fissure, and the pus was continuous with that lying in the meshes of the Sylvian pia and along the pial sheaths of the larger blood vessels entering the brain in this area.

Microscopic examination of the leptomeninges in the neighbourhood of the abscess (Sylvian fissure) and on the base of the brain immediately anterior to the optic chiasma showed diffuse purulent meningitis with septic thrombosis of branches of the middle meningeal and superficial middle cerebral veins

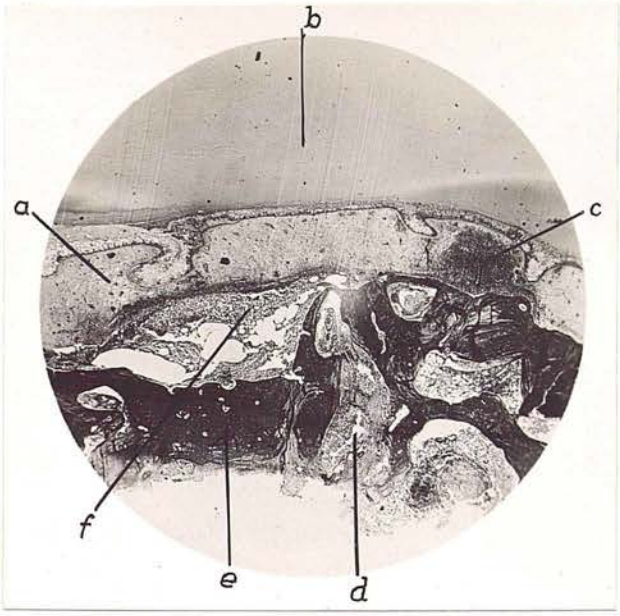


Fig.23.- Floor of l. sphen. sin. with septic thrombus in vein in bone; pus beneath the sinus mucosa and a small haemorrhage in it,

a. Muc. memb. b. Mucus in sphen. sin. c. Haemorrhage in mucosa. d. Thrombosed vein in bone. e. Bony floor of sphen. sin. f. Subperiosteal abscess.

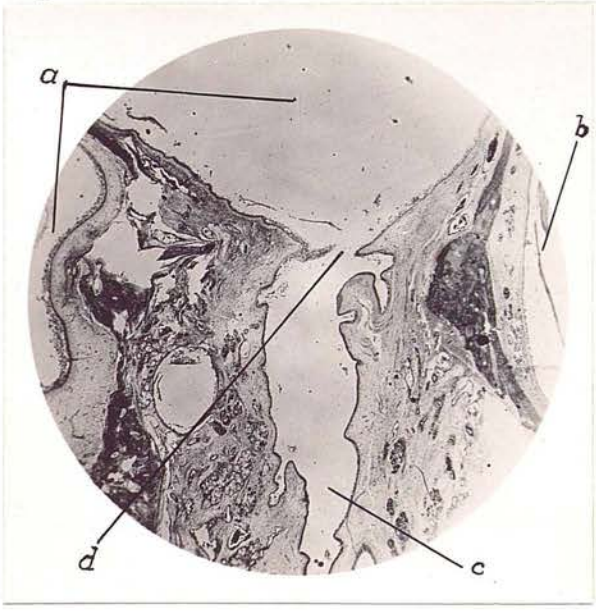


Fig.24.- Normal mucosa of r. post. ethm. cells and nasal mucosa.

a. R. post. ethm. cells.
b. L. nas. foss.
c. R. nas. foss.
d. Ostium ethm.

To face page 49.

(Fig.29). In some instances the wall of the vein had broken down and pus had escaped into the pial meshes. There was a diffuse leptomeningitis (Fig. 18).

Sections of the optic nerve at various planes in the optic canal and in the orbit showed purulent infiltration of the subarachnoid space and pial sheath surrounding the nerve (Fig.30).

Course of Infection.

As already noted (pg.27) the micro-organism may have reached the cavernous blood sinus from the primary focus by several methods. These will now be considered seriatim in relation to the present case.

(a) By Septic Thrombosis of Veins.- (1) Owing to the acute inflammation in and around the primary focus in the right ala nasi, injury of the endothelium of a small blood vessel (capillary or venule) may lead to thrombosis. The thrombus may extend backwards along the tributaries of the anterior facial into the angular vein, and thence reach the superior ophthalmic. The thrombotic process, having entered the latter, may, by a process of direct extension, finally involve the cavernous blood sinus.

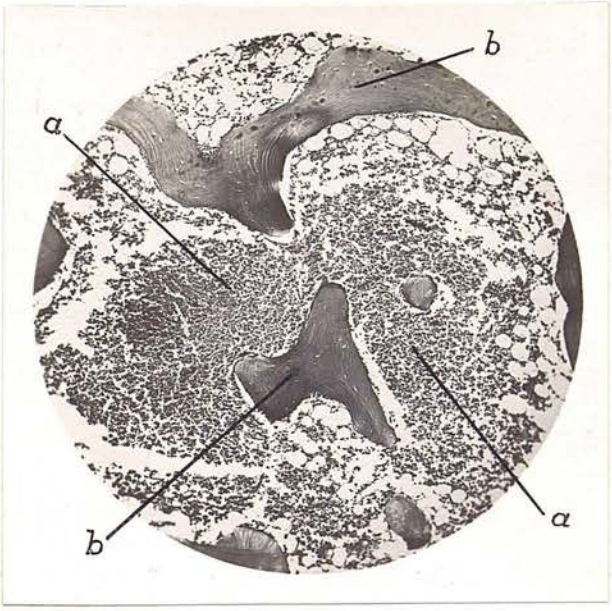


Fig.25.- Bone marrow in floor of sphenoidal sinus with pus in the diploë.

a. Pus in diploë. b. Bone.

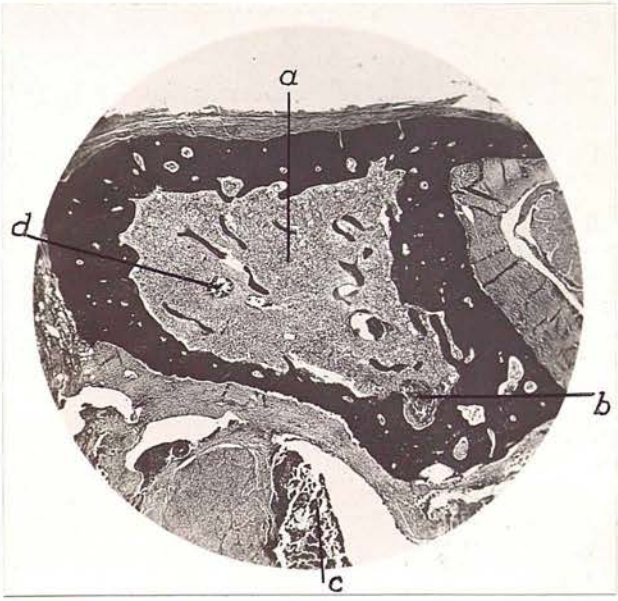


Fig.26.- R. anterior clinoid process with two veins completely thrombosed and one with commencing thrombosis.

a. Diploë. b. Thrombosed vein. c. Cavern. sin. d. Commencing thrombosis of vein.

To face page 50.

It seems more probable to the writer, however, that a small portion of the septic clot became detached at or near the junction of the angular and superior ophthalmic veins, and was carried as an embolus by the blood stream to the cavernous blood sinus, where it was arrested.

(2) There is, however, another possible mode of extension of the thrombotic process from the primary focus on the ala nasi to the superior ophthalmic vein. The thrombus, commencing in a small blood vessel in the immediate neighbourhood of the furuncle, may have extended along one of the small veins of the sub-cutaneous network and so directly reached the superior ophthalmic. This method of extension would seem to be more feasible than the spreading of the thrombus into such a comparatively large vein as the angular.

(3) Again, a minute portion of the septic thrombus in a small vein may have become detached and passed as an embolus along the anterior facial and angular veins, thus travelling against the direction of the general blood-flow for part of its course, a so-called "retrograde embolus". While this process is frequently advanced by authors to explain the spread of pathological processes in certain cases, the mechanism by which it occurs, in the case of

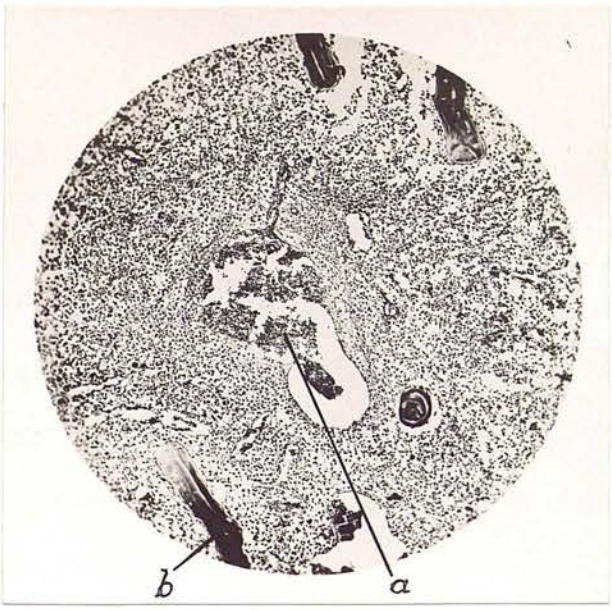


Fig.27.- R. ant. clin. proc. showing commencing septic thrombosis in a diploic vein.

a. Commencing thrombosis in diploic vein.
b. Bone.

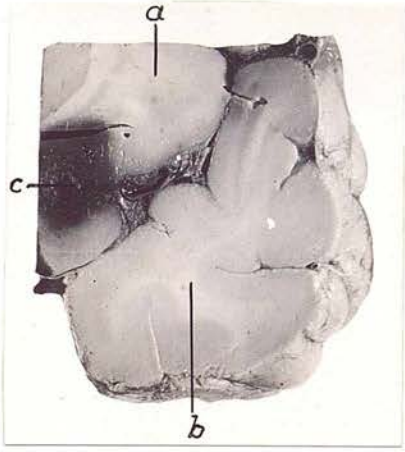


Fig.28.- Abscess in the right frontal lobe.

a. Frontal lobe. b. Temporal lobe.
c. Early abscess.

To face page 51.

veins, is exceedingly difficult to define. The process can be understood if a succession of waves is passing along the wall of a vessel. So far as is known, however, this does not occur in a vein, any alteration in the size of the lumen being due to a difference of volume of the blood passing through the vessel, and not, as is the case in the arteries, to contraction and relaxation of muscular walls.

(b) By the Micro-organism without Thrombosis of Veins.- Of 9 fatal cases of facial furuncle (5 being in the nasal vestibule) collected from the available literature, and in Cases II and IX of the present series in which bacteriological examination had been made, a staphylococcus was the responsible micro-organism in each instance. Although in this case bacteriological investigation to determine the causal micro-organism of the furuncle and septic thrombosis of the cavernous blood sinus was not made, it may be assumed that the infection was due to Staphylococcus pyogenes.

(1) The causal organism may have gained access to the lumen of one of the small veins of the subcutaneous network communicating with the superior ophthalmic vein, and thus have passed in the direction of the blood stream into the cavernous sinus.

(2) It is possible that the micro-organisms

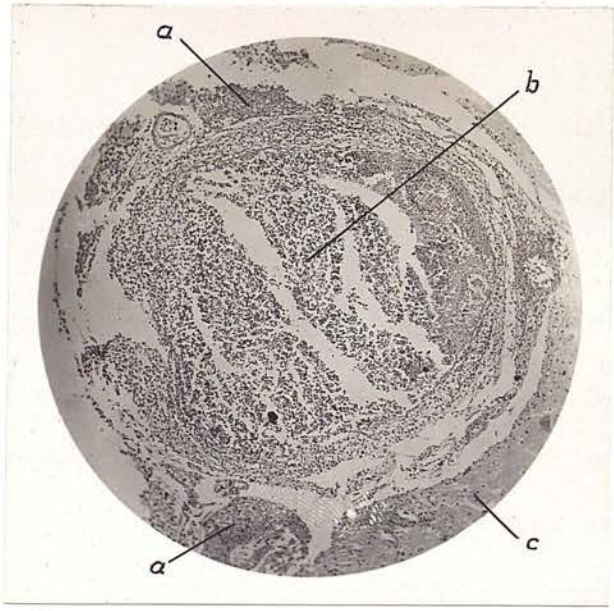


Fig.29.- Vein in pia mater of r. Sylvian fissure, with septic thrombosis of the vein and pus in the pial meshes.

a. Pia mater. b. Pial vein.
c. Cerebral cortex.

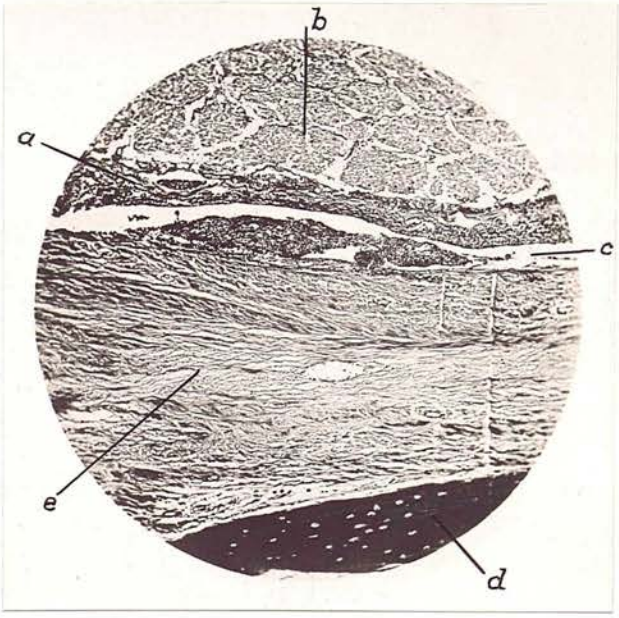


Fig.30.- R. optic nerve in its canal, with pus in the pial sheath and subarachnoid space.

a. Pial sheath. b. N.II. c. Subarach. space. d. Bone. e. Dural periosteal sheath.

To face page 52.

concerned in this infection may have invaded the perivenous lymph spaces and been carried by the to-and-fro motion of the lymph fluid into the lymph spaces round the ophthalmic vein. Thence they passed into the lumen of the vein and were borne by the blood stream into the cavernous sinus. If, however, the micro-organisms had travelled entirely in the lymphatic system, they would have passed into the internal maxillary lymph nodes, into which the lymphatic vessels of the orbit drain.

(3) The micro-organism itself may have been carried back as a retrograde embolus, so to speak, but the objection to this view is similar to that raised in the case of a retrograde embolus composed of infected blood clot.

(4) Lastly, it must not be forgotten that micro-organisms frequently show a peculiar selective action for certain tissues and parts of the body in particular cases. The factors governing the site of selection are quite unknown. It is conceivable that, in this case, the micro-organisms may have gained access to the general blood stream and finally settled in the cavernous blood sinus, causing a septic thrombosis.

Of all the possible modes of infection discussed above, the writer himself is inclined to favour the

view that septic thrombosis occurred in a venule in the neighbourhood of the furuncle. The thrombus extended thence along one of the small subcutaneous veins until it reached the superior ophthalmic, where a portion became detached as an embolus, which was arrested in the cavernous sinus.

When infection of the cavernous blood sinus occurred, septic thrombosis took place within it. The septic thrombotic process then extended in a direction retrograde to the normal blood stream. In this way, the veins of the orbit, some of the smaller veins of the deeper layer of the ethmoidal mucosa, the diploic veins, the spheno-parietal blood sinus, the smaller veins of the dura mater and the veins of the middle meningeal and middle cerebral system, became filled with septic thrombi. In association with the infection of the diploic veins, there arose an extensive osteomyelitis. The abscess found between the deep (periosteal) layer of the mucosa of the left sphenoidal air sinus and its bony floor was due to extension of the pus through the diploic veins in the immediate neighbourhood. Infection of the leptomeninges, along with the frontal lobe abscess, arose also as a result of the septic thrombosis of the meningeal veins.

Further, the microscopic examination of this

case illustrates very well the manner in which infection occurs round a vein containing a septic thrombus. The thin wall of the vein - in the case of smaller veins this is little more than a layer of endothelial cells - breaks down, and the pus with the micro-organisms escapes into the surrounding tissue; this process is seen in all the parts examined. The case further demonstrates a mode of general infection of the leptomeninges in cases of septic thrombosis of the cavernous blood sinus, a complication which is so frequently met with when this sinus becomes infected, and one which makes the prognosis most unfavourable in these cases.

In the absence of any evidence of a primary source of infection in the mucous membrane of the nasal cavities or in that of the accessory sinuses, the writer feels justified in concluding that the furuncle in the right ala nasi was responsible for the intracranial complications in this patient. The illness was of short duration, and all the pathological changes above described occurred within a period of one week.

CASE II. Furuncle of the Left Upper Lip: Septic Thrombosis of the Cavernous Blood Sinuses: Leptomeningitis: Death: Autopsy.

The following case bears a marked resemblance to the foregoing, both clinically and microscopically.

P.L., a girl, aged 13, was admitted on the 18th May, 1926, to a ward of the Royal Infirmary, Edinburgh, under the charge of Mr Struthers, F.R.C.S. to whom I am indebted for the following clinical notes.

The child was an inmate of an institution for mental defectives. In 1925, she had suffered from encephalitis lethargica, subsequent to which her mental state had been impaired. Her father and mother were alive and well. Her only brother died from perforation of a gastric ulcer.

The course of the present illness as ascertained from the nurse in attendance was as follows:- On the 8th May, ten days before admission, a "small sore" developed in the mucosal surface of the left side of the upper lip. During the week following, the lip became generally swollen and reddened, and on the 16th May the left cheek was similarly

Fig.31.- The illustration shows the patient on admission, on 18th May.

implicated, the swelling and redness extending on to the left lower eyelid. During the whole of this period the child was feverish, the temperature, on one occasion, being as high as 105°F. No rigors had been observed.

On the morning of the 18th May, the day of admission, the left eyeball became prominent and the doctor in charge of the Institution, who had seen the child forty-eight hours earlier, ordered her immediate removal to hospital.

On admission, the patient lay in bed in a drowsy state, but could be roused to answer questions. Temperature was 102°F, pulse 120, respirations 28. The whole of the upper lip was discoloured and markedly swollen (Fig.31). The mucous surface was covered with a layer of inspissated secretion, from beneath which, here and there, small beads of pus escaped. In the fold between the lip and the gum on the left side an irregular, ulcerated area was present; from this a track extended upwards beneath the lower part of the left cheek, and a probe passed along it detected bare bone in the incisor and canine fossae.

The left cheek was swollen and the overlying skin reddened, the left lower eyelid being similarly involved. The left upper eyelid was reddened and

oedematous.

The left eyeball was considerably proptosed and almost immobile, only a limited movement being possible. Chemosis was present on the lateral aspect of the ocular conjunctiva. The left pupil was somewhat dilated, reacting sluggishly to light. The moving fingers could be distinguished at a distance of one foot. The skin of the right upper eyelid was faintly discoloured and slightly swollen; the eyeball was not proptosed; chemosis was absent; the right pupil reacted actively to light.

Nasal and aural examination revealed no sign of suppuration.

Slight rigidity of the posterior cervical muscles was present; Kernig's sign was elicited on both sides but it was more pronounced on the left. On lumbar puncture, the cerebro-spinal fluid was definitely turbid and contained pus cells. A scanty growth of Staphylococcus albus was obtained from this sample.

On the following morning, 19th May, the condition of the right eye had become aggravated. The upper and lower eyelids had become oedematous and there was slight chemosis of the ocular conjunctiva; proptosis, however, was not present. Temperature was 104°F., pulse 148. During the day, coma became

pronounced and she died in the evening.

The duration of the illness, dating from the first appearance of the sore on the lip, was ten days.

Autopsy.- Permission was obtained to examine the whole body. At the post-mortem the left eyeball was still proptosed. An excess of cerebrospinal fluid was present. Pus was not evident in the pia-arachnoid meshes over the vertex of the brain, but it was present in and around the lower third of the left Sylvian fissure, on the anterior pole of the corresponding temporal lobe, and on the lower surface of both cerebellar hemispheres. On the base, pus was infiltrating the hypophysis. The left lateral sinus contained septic clot, and pus was present in the left inferior petrosal sinus. The frontal and maxillary air-cavities were healthy.

A number of the internal organs showed general pyaemic infection, small abscesses being present in the lungs, kidneys and spleen; early pericarditis was present.

Bacteriology.- Swabs which were taken, shortly after admission, from the pus which oozed from the swollen upper lip and from a track which passed upwards in front of the maxilla gave a growth of Staphylococcus aureus. A scanty growth of the same

micro-organism was also obtained from the cerebro-spinal fluid drawn off on the day of admission.

From swabs taken at autopsy, a pure growth of Staphylococcus aureus was obtained from the meningeal exudate on the base of the brain, from the thrombus in the left lateral sinus, and from one of the small abscesses in the spleen.

Preparation of Material for Microscopic Examination.- A large block was removed from the base of the skull. This included not only the body of the sphenoid bone with the superimposed structures, the posterior part of the ethmoid mass and adjacent nasal cavities, but also the contents of both orbits. A portion of the left half of the upper lip was excised and prepared for examination.

The large block was placed in Parenny's solution After decalcification, it was subdivided in the coronal plane into portions suitable for embedding in paraffin.

Report on the Material examined Microscopically.

1. The Lip. The whole tissue of the upper lip was densely infiltrated by polymorphonuclear leucocytes, large mononucleated and small mononucleated cells. Numerous small abscesses were present.

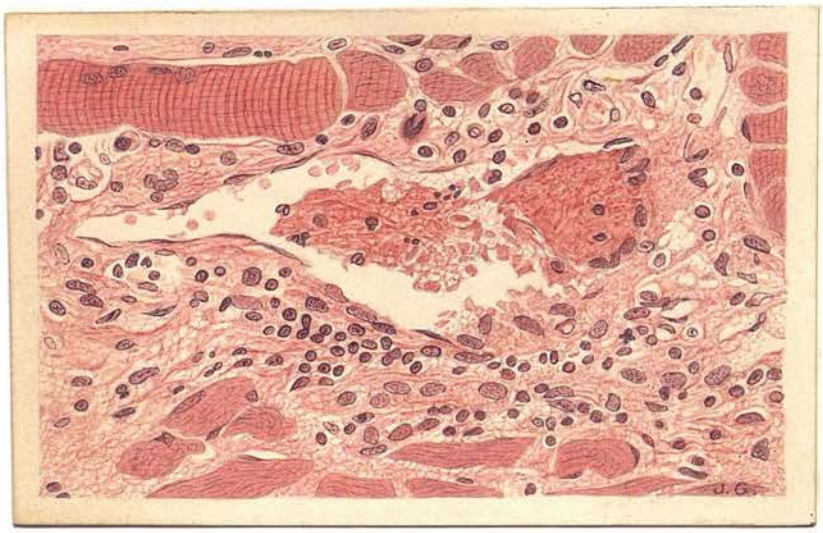


Fig.32.- From a section of the primary focus in the lip showing an early stage of thrombosis in a venule. Towards the right the lining endothelial cells are swollen and proliferating; blood clot has been deposited upon them, but the thrombus does not yet fill the whole lumen of the vessel. (Stained by haematoxylin and eosin.)

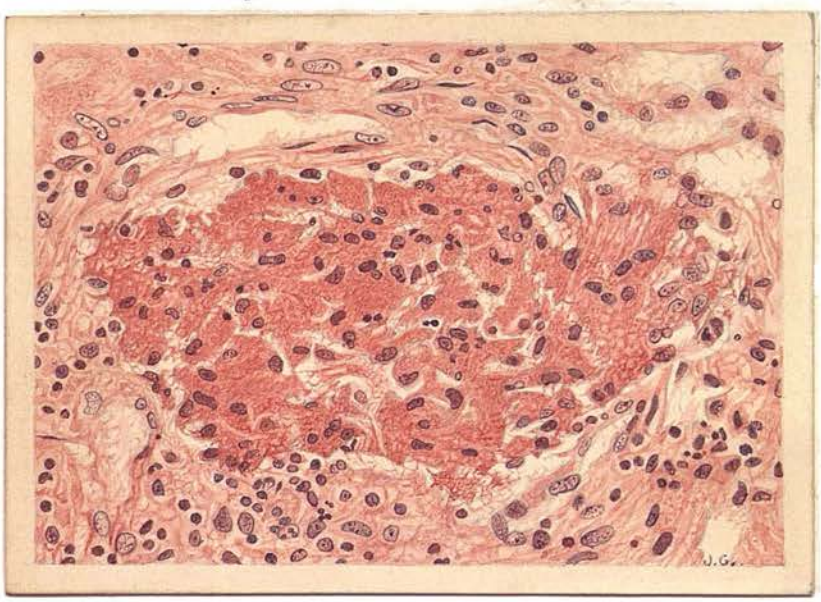


Fig.33.- From a section similar to the above showing a further stage in the process of thrombosis. The lumen of the venule is filled with thrombus which has been invaded by mononucleated cells derived from the endothelial lining of the vessel and by polymorphonuclear leucocytes. (Stained by haematoxylin and eosin.)

To face page 60

The smaller blood vessels showed various stages of thrombus formation (Figs.32,33). In some the thrombus was attached to one part only of the wall and did not fill the whole lumen; it consisted of fibrin with red blood corpuscles entangled in the meshes and contained a certain number of polymorphonuclear leucocytes. At the point of attachment of the clot, the vascular endothelium was swollen and proliferating and in certain instances numerous proliferated endothelial cells were scattered through the thrombus. Again, in other vessels the polymorphonuclear leucocytes in the clot were numerous; in some of these the clot had disintegrated and the vessel was surrounded by numerous polymorphonuclear leucocytes.

2. Cavernous Blood Sinuses. Both the cavernous and the circular blood sinuses were full of pus. The pus had infiltrated into the tissues surrounding the trunks of the second division of the Fifth Cranial Nerve in the outer wall of the sinus. Some of the Haversian systems in the bone adjacent to the medial wall of the right cavernous blood sinus were infected and a few areas of early infection were present in the underlying red marrow.

3. The Leptomeninges and Dura Mater. In sections taken from the base of the brain in the neighbourhood of the optic chiasma, of the Sylvian

fissure, and of the folia of the cerebellum of the left side, the pial veins were dilated and the leptomeninges contained a large amount of exudate. The exudate consisted of fibrin and, in the first situation, of large, rounded, mononucleated cells; whereas in the last two situations, polymorphonuclear leucocytes were the predominant cells. The pus extended into the horizontal limb of the left Sylvian fissure and into the areolar tissue around the third division of the Fifth Cranial Nerve.

In sections taken from the outer surface of the left parietal lobe, the leptomeninges contained fibrin and a large number of diffusely scattered mononucleated cells, but few polymorphonuclear leucocytes. In the leptomeninges of the corresponding area on the right side, only an occasional mononucleated cell was demonstrated.

On the right side thrombosed veins, tributaries of the superior petrosal sinus, were present in the fold of dura mater situated at the junction of the middle fossa and the adjacent edge of the dorsum sellae. In the sections examined, no veins were found in the dura mater attached to the dorsum sellae. On both sides, extensive thrombosis had occurred in the dural veins of the middle fossae.

4. <u>The Diploë</u>. The bone in the sections

consisted of the body and great wing of the sphenoid. On the right side the red marrow spaces in the body of the sphenoid were not infected; on the left side, however, extensive infection had occurred in the root of the great wing of the sphenoid lying beneath the dura mater.

5. The Orbits. The series of coronal sections were made from before backwards, commencing on a plane passing through the posterior part of the globe in front of the optic nerve. In the left orbit, septic thrombosis of the veins had occurred and, especially towards the apex, the pus had escaped from the veins into the fat, forming numerous microscopic abscesses. The septic thrombi were continuous with those in the cavernous blood sinus.

In the right orbit a similar condition of the veins was present, but the pus was confined to the lumen. On this side the thrombotic process had not passed so far forward in the orbit as on the left side.

6. Post-pterygoid Region and Foramen lacerum. On the left side, in sections of the post-pterygoid region, some of the smaller veins showed early septic thrombosis and an abscess was commencing to form in an area of fibrous tissue. In no other instance

had the infection spread beyond the walls of the veins into the surrounding tissue. A lymph node was present in the sections; marked hyperplasia of the lymphoid elements had occurred; in the lymph sinuses of the node and in the lymphatic vessels around it a large number of small mononucleated cells were seen. On this side, the veins of the carotid plexus were not thrombosed.

On the right side, the structures in the post-pterygoid region showed no septic infection, but a certain number of the small veins of the carotid plexus contained early septic thrombi.

7. The Nasal and Accessory Cavities: The Sphenoidal Air-Sinuses. The mucous membrane on the floor of both cavities was oedematous, the tissue spaces being dilated; the mucosa was sparsely infiltrated by larger and smaller rounded mono-nucleated cells. The mucous membrane of the medial, lateral and superior walls showed no pathological changes.

The Ethmoidal Air Cells. On both sides the mucous membrane of the anterior and posterior ethmoidal air cells was oedematous in places, the changes being similar to those in the mucosa lining the floor of the sphenoidal cavities.

The Left Maxillary Air Sinus. The mucosa covering the roof of this cavity was normal.

The Nasal Mucous Membrane. The respiratory nasal mucosa showed a certain amount of infiltration by mononucleated cells. On both sides, the olfactory sulcus was narrow and contained desquamated epithelial cells and mucus; the lining membrane was intact and actively secreting mucus. The olfactory perineural sheaths showed no cellular infiltration.

Origin and Progress of the Infection.

As already stated, the present case resembles closely that of Case I. In both instances the infection of the cavernous blood sinus was by way of the anterior route; in the first, from a furuncle of the nasal vestibule, and in the second from a septic focus in the upper lip.

It is certain in the present case that the left cavernous sinus became thrombosed before the right. Not only was the primary focus on the left side of the upper lip and the left eye only was proptosed, but both at autopsy and histologically, infection had occurred more widely and to a greater degree on the left than on the right side.

Septic thrombosis having occurred in a venule of the upper lip, it probably extended, for similar

reasons to those given in Case I, by way of the left ophthalmic veins to the left cavernous blood sinus. Thence the septic thrombotic process extended along the circular sinus to the right cavernous sinus, and through the left inferior petrosal to the lateral sinus on the same side. Extension also occurred in a direction retrograde to the normal blood flow. In this way the pial veins became infected and gave rise to acute purulent leptomeningitis. By the same retrograde process, diploic and orbital veins were similarly infected, in both instances producing small peri-venous abscesses. The route of extension, as above outlined, has already been fully argued in Case I.

The abscesses found at autopsy in the lungs, kidneys, and other organs of the body were the result of micro-organisms in the general blood stream and their arrest at these sites. Hence, in addition to local spread of infection from the cavernous blood sinus by a progressive continuous septic thrombus, general infection of the organs had occurred.

That the nasal accessory air cavities showed no marked infection was further evidence that the lip was the primary focus. The writer is not inclined to attach any etiological importance to the presence

of pus in the nasal cavities, since in persons seriously ill and dying of septic conditions preceded by coma, it is not uncommon to find purulent contents in the nasal cavities.

In the present case, the stages of thrombosis in the small blood vessels in the primary lesion can be demonstrated, although, naturally, these are not the actual venules from which the infection first spread to the cavernous blood sinus. The initial local infection in the lip has extended and, in the course of its progress, transfusion of the bacterial toxins has damaged the endothelium of the small venules, the damage being manifest by swelling of the lining cells. On the swollen endothelial cells, fibrinous clot has been deposited and, later, has become infected by bacteria.

CASE III. Acute Inflammation of the Ethmoidal and Sphenoidal Sinuses (bilateral): Cavernous Sinus Thrombosis: Acute Leptomeningitis: Operation: Death: Autopsy.

W.E., male, aged 26, was admitted to the Royal Infirmary, Edinburgh, on 20th January, 1921, under the care of Dr W.T. Gardiner, F.R.C.S.E., to whom I am indebted for the following clinical notes. The illness commenced five days previously with symptoms suggesting influenza - headache, general malaise, and pains in the back and limbs. The temperature varied from 102°F. to 103°F., with rapid pulse.

Twenty-four hours after the onset of symptoms, he complained of pain in the left eye, which began to project forwards. Within forty-eight hours the pain on the left side had subsided to some extent, but the right eye became painful and slightly proptosed.

When seen by Dr Gardiner seventy-two hours after the initial symptoms had commenced, the left eye was proptosed and immobile, save for a slight external deviation. The right eyeball was also proptosed and immobile. Visual acuity was good, as tested by the fingers.

The nasal mucous membrane was congested, but no pus was seen in either cavity. The nasopharyngeal

mucous membrane was intensely congested. The temperature continued elevated, between 102° and 103°F. and there was occasional sweating. A history of long continued nasal catarrh was obtained.

On admission, the ethmoidal and sphenoidal sinuses were opened up under local anaesthesia. No pus was found. Lumbar puncture revealed clear cerebrospinal fluid under normal pressure.

Death took place within six hours of the operation.

Autopsy.- The vessels on the surface of the brain were congested, but there was no meningeal exudate. Both cavernous sinuses contained pus, which extended into the anterior end of each superior petrosal sinus. Films from the pus showed Gram-positive streptococci. Numerous abscesses varying from a pin-point in size to 1 cm. in diameter were scattered through both lungs, the larger abscesses being surrounded by a zone of intense hyperaemia. A dirty yellow exudate was found in the pleural cavities.

Several petechial haemorrhages had occurred under the parietal and visceral layers of the pericardium.

A block of bone containing the sphenoidal and

ethmoidal air cells was removed for microscopical examination. After decalcification in Parenny's solution, it was divided into two portions in the coronal plane through the anterior lobe of the pituitary body. Both of these blocks were embedded in paraffin and serial sections were made in the coronal plane from before backwards.

Report on the Material examined Microscopically.

Sections taken from the front portion of the anterior block showed both nasal cavities and the posterior ethmoidal cells partly destroyed by the surgical operation, and the mesial portion of both orbital cavities.

The posterior block comprised both sphenoidal air sinuses and their lateral bony walls and roof, both cavernous blood sinuses and associated structures, the pituitary body, and underlying intercavernous veins.

The various histological appearances in this Case are so similar to those in Case I, that it has been thought unnecessary to have illustrations prepared from the sections.

(1) Nasal Mucous Membrane.- Owing to the previous surgical interference, the ethmoidal and nasal cavities were opened up and the walls were broken

down. In the ethmoidal region of the nose a small portion of mucosa which remained was not thickened. The mucous glands were numerous and active. The lining columnar epithelium of the mucous membrane was intact and there was no undue infiltration of the mucosa by cells of an inflammatory type. The middle coat of many of the arteries was thickened, this being due partly to the muscular elements and partly to the presence of fibrous tissue.

(2) Posterior Ethmoidal Cells.- The large cavity formed by the removal of the naso-ethmoidal wall contained blood clot. There was considerable haemorrhage into the layers of the mucosa, this being mainly of traumatic origin.

The mucosa, for the most part, was markedly oedematous. It was partially infiltrated by cells, most of which were mononucleated in type, but there was a certain number of polymorphonuclear leucocytes. The smaller blood vessels were somewhat dilated, but no active diapedesis was taking place through the walls. The lining columnar epithelium was intact, but in certain areas it had been detached by operative interference. These changes were more marked on the right than on the left side.

No inflammatory changes were present in the bone marrow or Haversian spaces of the ethmoidal cell walls.

(3) The Orbits.- The small amount of orbital tissue present on the left side contained two branches of one of the ophthalmic veins. The larger of the two branches was filled by septic clot, the peripheral portion of which was undergoing softening and was densely infiltrated by polymorphonuclear leucocytes; the smaller branch was filled with pus and in the lower portion the wall had broken down and the pus had spread into the surrounding fatty tissue.

In the right orbit, in the tissue present was one small branch of the ophthalmic vein; this showed commencing septic thrombosis. The loose fatty tissue of the orbit was infiltrated in places by polymorphonuclear leucocytes. The small portion ~~present~~ of the bony roof of the orbit which was present in the sections showed no inflammatory changes.

The upper lateral portion of the pial sheath of the left optic nerve showed some infiltration by polymorphonuclear and mononucleated cells. In the sheath of the right nerve were small areas which were rather more cellular than normal, the cells being mostly large mononucleated in type, but an occasional polymorphonuclear cell was present in some of these areas.

(4) The Sphenoidal Air Sinuses and Cavernous Blood Sinus.- From the posterior block a series comprising 840 serial sections was made from before backwards. The anterior sections of the series showed both sphenoidal air sinuses, but those cut more posteriorly showed the left side only, this being the larger cavity.

The pathological changes in the mucous membrane of the larger (left) sinus were seen throughout its whole extent. The mucous membrane was very oedematous and the small blood vessels were dilated. There were numerous petechial haemorrhages and the mucosal layers were infiltrated by polymorphonuclear leucocytes and by small and large, round or oval, mononucleated cells. The lining columnar epithelium was intact and the various types of infiltrating cells were passing towards the surface between the columnar cells. The cavities contained a large amount of traumatic haemorrhage. In the right (smaller) sphenoidal air cavity the mucous membrane was oedematous in places only. For the most part it was not thickened. In the anterior sections, portions of the mucous membrane had been detached from the lateral and superior wall of the cavity at the surgical operation carried out shortly before death. There were many traumatic haemorrhages into the layers of

the mucous membrane which remained attached. The blood vessels were dilated and the mucosa was infiltrated by polymorphonuclear leucocytes and small and large, round or oval mononucleated cells. In some of the anterior sections a small vein in the mucosa lining the septal wall was filled completely by septic clot. A larger vein showed a septic thrombus attached to its wall, but only partially filling the lumen. On tracing back the larger vein, its lumen was filled completely by septic thrombus, and one of its tributaries, also thrombosed, was seen passing through the compact bone into the red marrow of the body of the sphenoid. On tracing backwards through the series of sections, the small mucosal vein described above along with other small veins similarly filled with septic thrombi were found to open into the larger vein described previously.

In both sphenoidal air sinuses small abscesses were present between the deep layers of mucous membrane and bony wall. In the left sinus these were situated in the floor; in the right sinus, in the roof.

A large Haversian space adjacent to the small abscess in the right sphenoidal sinus contained a considerable amount of pus, and pus was present in

two of the veins of this space.

(5) The Bone Marrow.- In the series of sections red marrow was present in the dorsum sellae lying below and lateral to the pituitary body, in the lateral walls of both sphenoidal air sinuses, and in the bone forming the floor of the larger (left) sinus. In all these situations, collections of pus were present in the marrow. The bony roof of the sphenoidal air sinus, composed of a thin layer of compact bone, was traversed by Haversian canals, but did not contain bone marrow. The loose connective tissue of the larger Haversian canals was cellular, but no definite thrombosis of Haversian veins had occurred, nor were polymorphonuclear leucocytes present in the areolar tissue. A vein in the deep layer of the dura mater covering the dorsum sellae was filled with septic clot, but this was continuous with pus lying in the bone marrow.

(6) Meninges.- The remnants of pia-arachnoid which still remained attached to the dura mater were densely infiltrated by polymorphonuclear leucocytes and large and small, round or oval, mononucleated cells. The loose areolar tissue around the bundles of the fifth cranial nerve was also infiltrated with pus.

Many of the small veins in the dura mater over the dorsum sellae and in that portion of the medial wall of the middle cranial fossa present in the sections contained septic thrombi. These veins were situated for the most part in the deep periosteal layer of the dura mater. Around the thrombosed veins the layers of dura mater were infiltrated by polymorphonuclear leucocytes and diapedesis of these cells through the walls of the veins was active.

(7) The Cavernous Blood Sinuses.- Both cavernous sinuses were filled with septic clot. In most of the spaces the clot was infiltrated throughout by polymorphonuclear leucocytes, but in some of them the centre of the clot was composed of red blood corpuscles and the periphery had undergone partial liquefaction, the material being densely infiltrated by polymorphonuclear leucocytes.

(8) Pituitary Body.- Some of the veins in the posterior part of the pituitary body (pars nervosa) contained septic clot. The pituitary tissue in the immediate neighbourhood of the thrombosed veins was infiltrated by polymorphonuclear leucocytes.

Summary and Conclusions.- In this case the clinical history and examination pointed to an acute inflammation, possibly following influenza, which

affected the sphenoidal air sinuses. This was borne out by microscopical examination, the mucosa of these cavities showing acute widespread inflammatory change. That this change was not secondary to the thrombosed veins found in the mucosa is shown by the fact that the inflammation was diffuse and not localised to the neighbourhood of the thrombosed veins.

Arguments similar to those advanced in Case I make it certain that the actual mode of infection of the cavernous sinus from the primary focus, namely the sphenoidal mucosa, was undoubtedly by the blood stream.

The question raised in that Case as to whether the micro-organisms (staphylococci) gained access to the cavernous blood sinus by means of or without the intervention of a spreading venous thrombosis, applies equally to the present case.

Infective thrombosis of one cavernous blood sinus (the left) having occurred, the thrombotic process spread along the communicating circular sinuses to the other sinus and along the venous tributaries of both cavernous sinuses, giving rise to widespread osteomyelitis, leptomeningitis, orbital cellulitis, and small abscesses under the periosteal layer of the sphenoidal mucosa.

The abscesses in the lungs were an expression

of a general pyaemic condition.

It might be maintained that the septic thrombosis seen in some of the veins of the sphenoidal mucosa was primary and due to the acute inflammation of the mucous membrane, and that the thrombotic process had extended along these into the cavernous sinus, thus causing thrombosis of its blood spaces. Widespread thrombosis of veins, however, has been found, namely, in the orbital cavity, in the dura mater and in the red bone marrow not only in the walls of the sphenoidal air cavities but in remote areas, e.g. basisphenoid, dorsum sellae, etc.

It is certain, therefore, that in the majority of instances in which thrombosis had occurred in the veins of the mucous membrane of the sphenoidal sinus, this change was a secondary spread from the thrombosis of the cavernous sinus (retrograde thrombosis) Whether any one particular vein in the mucosa was thrombosed prior to infection of the cavernous sinus, is quite impossible to determine.

CASE IV. Acute Middle Ear Suppuration (Left): Acute Mastoiditis: Septic Thrombosis of Cavernous Blood Sinus: Leptomeningitis: Cortical Operation on Mastoid Cells: Death: Autopsy.

Unlike the foregoing cases, the present one is an example of cavernous sinus thrombosis arising as a result of acute inflammation in the middle ear and mastoid cells. It is introduced into the Series since it illustrates that the fulminating type of thrombosis may occur when the primary focus is in the middle ear cleft and, further, that the results of secondary thrombosis of tributary veins of the cavernous sinus can give rise to marked and widespread results. Hence, unless a thorough microscopical examination be made of the tissues, erroneous conclusions may be drawn as to the site of the primary focus from which the cavernous blood sinus has become affected.

D. McL., boy, aged 7, was admitted on 14th December, 1928, to the Ear and Throat Department, Royal Infirmary, Edinburgh, under the care of Dr J. S. Fraser, F.R.C.S.E., to whom I am indebted for the following clinical notes.

Four weeks previously the child had measles.

On 8th December, six days before admission, some swelling of the left cheek was noticed; in the opinion of the doctor, this was due to a diseased tooth. Acute pain in both ears was also complained of, but no aural discharge was then present nor was any history obtained of previous ear trouble.

On 11th December, the child had a rigor associated with vomiting and high temperature.

On 13th December, the upper and lower eyelids on both sides were oedematous, the swelling being more pronounced on the left side. The patient had frontal headache.

On 14th December, on admission to hospital, the child was delirious and unable to answer questions. His general aspect suggested the existence of meningitis. The temperature was 104°F. and pulse rate 140; the tongue was furred; neck rigidity was present, but no Kernig's sign was elicited. There was proptosis of both eyeballs.

The left external acoustic meatus was full of pus; the tympanic membrane was red and bulging, but no perforation was visible. Pressure upon the left mastoid process was resented. The right tympanic membrane was red and bulging.

Lumbar puncture yielded cerebrospinal fluid which was clear, but under considerably increased pressure.

Notwithstanding the serious condition of the patient, operation was performed on the left ear. All the mastoid cells contained pus. The sigmoid portion of the transverse sinus was freely exposed and its dural wall had a normal appearance; the dura mater of the middle fossa was exposed and was also normal. Pus was obtained on paracentesis of the right drumhead.

On 15th December, the temperature was still high and the child was very restless.

Lumbar puncture yielded cerebrospinal fluid which was at first cloudy, but rapidly became blood-stained. Examination showed 337 cells per c.mm., many of which were red blood corpuscles, increase of protein content, and a colloidal gold reaction of 0011200000.

A blood culture made on this date gave no growth of micro-organisms.

The patient died at 8 p.m., twenty-four hours after admission.

Autopsy.- Permission to examine the head only

was obtained. The post-mortem was conducted 16 hours after death. No oedema of the eyelids or protrusion of the eyeballs was present. To the naked eye, the cerebral cortex showed no generalised meningitis. On removing the brain, an extensive subdural haemorrhage was found in the floor of the three cranial fossae, most pronounced in the anterior and middle, and a thin layer of pus was present in the interpeduncular space. On the inferior surface of the tip of the left temporal lobe there was a definite deposition of pus and the surface of the brain was ulcerated over a small area.

After washing off the blood clot, the cerebral surface of the dura mater covering the left great wing of the sphenoid was seen to be discoloured. On this discoloured area, the tip of the left temporal lobe had been superimposed.

On removing the tissue for microscopical examination (see below) when the orbital tissues behind each eyeball were divided, beads of pus escaped from the ophthalmic veins and fatty tissue.

Bacteriology.- Direct smears of the pus over the inferior surface of the tip of the left temporal lobe and of the pus in the interpeduncular space showed numerous Gram-negative bacilli of the type of

Bacillus influenzae, Pfeiffer. Only the ordinary culture media were employed and no growth was obtained.

Preparation of the Material for Microscopical Examination.- A block of bone was removed from the base of the skull. This included the body of the sphenoid bone with the superimposed structures, the posterior part of the ethmoidal labyrinths and adjacent nasal cavities, and the contents of both orbits. The block was placed in Parenny's solution and, after decalcification, it was subdivided in the coronal plane into portions suitable for embedding in paraffin.

Report on the Material examined Microscopically.

1. The Cavernous Blood Sinuses.- On both sides the blood spaces of the cavernous sinuses were full of pus. A large amount of pus was present in the loose tissue in the lateral wall of the sinuses; this surrounded the nerve sheaths, but the pus had not ruptured into the nerve bundles. Beneath the pituitary body the intercavernous dural veins were filled with pus continuous with that in the spaces of the cavernous sinuses.

2. The Pituitary Body.- The left half of the

pituitary body was undergoing necrosis.

3. The Leptomeninges.- The venules were widely dilated and an acute purulent leptomeningitis was present.

4. The Bone.- Almost the whole of the diploë in the body of the sphenoid bone behind the plane of the air cavities was necrosed. There was no reaction in the narrow marginal zone of red marrow surrounding the necrosed portion.

More anteriorly where the bone was forming the lateral walls of the sphenoidal air cavities, necrosis was not so diffuse in the diploë. In some areas large thrombosed veins were present in which suppuration had taken place and in some instances the walls of the veins were breaking down and pus was escaping into the surrounding diploic tissue.

The diploë in the bone forming the floor of the sphenoidal air cavities was necrotic and collections of pus were present in places.

5. The Carotid Venous Plexuses.- These were examined at the upper, intracranial, end of the bony canal. On the right side the canal was nearly full of pus and only a few comparatively large veins of the plexus persisted. One of these was thrombosed but the clot was not septic; two other veins,

however, were full of pus.

On the left side, small veins of the carotid venous plexus persisted in the wall of the artery in the canal. They were dilated and there was active diapedesis of polymorphonuclear leucocytes through their walls. The areolar tissue of the adventitial coat of the artery was infiltrated by polymorphonuclear leucocytes. Three of the larger veins contained septic thrombus and in the lateral bony wall of the canal there was a subperiosteal abscess.

6. The Eustachian Tubes.- The Eustachian tube in relation to the carotid canal on the left side was present in the sections examined. Its columnar lining was intact; the subepithelial tissue showed a certain amount of infiltration by mononucleated cells; the lumen contained desquamated epithelium and polymorphonuclear leucocytes. The thin intervening bony septum between it and the carotid canal was formed of compact bone without marrow spaces and the Haversian canals were not infected.

On the right side the sections were on a somewhat different plane and the Eustachian tube was not present.

7. The Orbital Fat.- Sections of the tissues from both orbits demonstrated small abscesses in the

fat, and also pus in the larger veins.

8. The Sphenoidal Air Sinuses.- In the right sphenoidal air-cavity the mucous membrane was thickened and polypoid; there was considerable oedema of the tissue with great dilatation of the blood vessels. The layers of the mucosa were infiltrated by numerous large, round, mononucleated cells and polymorphonuclear leucocytes.

In the lateral and medial (septal) walls of the air cavity, large dilated blood and lymph spaces were present, the condition being a cavernous haemo-lymph-angeioma. Considerable haemorrhage had occurred into the mucosa. There were numerous subperiosteal abscesses due to secondary thrombosis of veins. In one area a large mucosal vein entering the bone of the floor was filled by a septic thrombus.

The lumen of the air-cavity contained muco-pus.

All the pathological changes were of an acute character, there being no signs of chronic inflammation. The acute septic process had no etiological relationship to the haemo-lymph-angeioma.

In the left sphenoidal air-cavity, of which only the posterior portion was present in the sections examined, there was a lymphangiomatous condition. Subperiosteal abscesses were also present, many of

them being continuous through the Haversian spaces with pus in the adjacent bone marrow.

Commentary.

In this case of acute inflammation of the left middle ear cleft, the patient developed septic thrombosis of the cavernous blood sinuses and acute haemorrhagic leptomeningitis. Extensive infection of the body of the sphenoid bone, of the mucous membrane and bony walls of the sphenoidal air cavities, of the carotid bony canal - most marked on the right side, of the orbital veins and fatty tissue on both sides had also occurred.

The first point to be decided is the primary focus of the infection, namely, the sphenoidal air cavities or the middle ear. In the former, no chronic changes were found and therefore there is no question of an old-standing inflammation having recently been stimulated into acute activity. As septic thrombosis had occurred in many large veins of the sphenoidal sinus mucosa and as the acute inflammation in the mucous membrane was not of a degree sufficient to produce thrombosis in veins of this calibre, the venous affection was not primary but secondary to the cavernous sinus infection. Moreover,

changes similar to these were demonstrated, for example, in Case I, in which the sphenoidal air cavity could be quite definitely excluded as the primary focus.

By elimination of the sphenoidal air cavities, there remains the middle ear and mastoid cells as the primary focus.

The route and method of transmission of the infection from the middle ear cleft to the cavernous sinus must be a matter of conjecture in this case, as unfortunately the transverse and petrosal sinuses were not examined either at the autopsy or later. In the majority of recorded cases in which the middle ear and mastoid cells have been the primary focus, the infection has travelled by way of the transverse and petrosal sinuses.

The carotid venous plexus as an alternative route of infection from the middle ear cleft can be, in the writer's opinion, definitely excluded in the present instance. In the first place, the inflammatory changes in the canal were more widespread and advanced on the side opposite the initial lesion; secondly, on the side of the primary lesion only some larger veins were thrombosed, the smaller ones actively reacting to infection in the areolar tissue

of the canal; thirdly, the diploë in the wall of the canal was markedly infected and the sepsis within it was in all probability secondary to this. The pathological process present here, therefore, was the same as that in the walls of the sphenoidal air cavities.

Septic thrombosis of the sphenoidal sinuses having occurred, the process extended along their tributaries in a direction retrograde to the normal blood flow. Thus there arose osteomyelitis over a wide area, subperiosteal and mucosal abscesses, orbital abscesses, leptomeningitis, etc.

In concluding the discussion, reference must be made to the haemorrhage into the mucous membrane of the right sphenoidal cavity and into the leptomeninges. In the former site it was associated with the haemangeioma and was probably in part an expression of active reaction to the infection of the mucous membrane and in part due to thrombosis of its efferent veins. As the microscopical preparations of the leptomeninges did not show any similar angeiomatous condition of the pial blood vessels, the extensive subdural haemorrhage found at autopsy must be interpreted as an expression of the infection by Bacillus influenzae, Pfeiffer.

Case V. Chronic Suppurative Otitis Media (Left): Acute Mastoid Infection and Perisinus Abscess: Septic Thrombosis of Left Transverse Sinus and Inferior Petrosal Sinus: Septic Thrombosis of both Cavernous Blood Sinuses: Leptomeningitis: Operation: Death: Autopsy.

The present case is introduced into the series since the progress of infection is typical of those in which septic thrombosis of the cavernous blood sinus occurs from a primary focus in the middle ear and mastoid cells. The pathway by which the infection had reached the cavernous sinus was demonstrated at autopsy and the subsequent progress of infection has been demonstrated and argued in similar previous cases of the series. Microscopical examination of the tissues implicated was not necessary, therefore, to elucidate the course of the disease.

A.B., boy, aged 15, was admitted to the Ear and Throat Department of the Royal Infirmary, Edinburgh, on 21st June, 1929, under the care of Dr G. Ewart Martin, F.R.C.S.E., to whom I am indebted for the following clinical notes.

For the past seven years, the patient had had

discharge from the left ear; during this time the discharge had ceased for short periods.

During the week before admission, the discharge from the ear was more copious. Three days before admission the patient began to vomit and had continued to do so intermittently. On the day prior to admission, he developed pain over the left side of the head, extending to the occiput.

On 21st June, when admitted to hospital, the patient was in a somewhat stuporous condition; when spoken to, however, he responded and answered questions fairly readily and with accuracy. There was no loss of word memory. The temperature was 102·8 °F. and the pulse rate 120. The pupils were equal, normal in size and reaction, and there was no spontaneous nystagmus. Slight neck rigidity was present and a definite Kernig's sign was elicited, but the reflexes were normal. The left ear contained granulations and there was a foul-smelling discharge from it. (No hearing tests are recorded.) On lumbar puncture, clear cerebrospinal fluid was obtained and it was not under increased pressure.

The complete operation was performed on the left mastoid process and middle ear. The process was pneumatic in type; pus was present just under the

bony cortex and the tip of the process was necrosed. The sigmoid portion of the transverse sinus was freely exposed and a perisinus abscess evacuated; granulations were present on the sinus wall, but there was free bleeding from the emissary vein and it was concluded that the transverse sinus was not thrombosed.

On 22nd June, the temperature, which had gradually fallen to normal, rose in the afternoon to 103°F., falling during the night to 100°F. The patient had a restless night.

On 23rd June, in the morning, the upper eyelid on each side was oedematous, the condition being more marked on the left side. Chemosis of the left conjunctiva supervened, followed by a similar change in the right eye; slight proptosis of both eyeballs occurred. During the day the temperature rose to 103°F., and then fell suddenly to normal.

On 24th June, the patient's condition was much worse and he became semiconscious. The pupils reacted faintly to light; it was impossible to ascertain accurately whether any movements of the eyeball could be made. The temperature was high and death occurred at 7.30 p.m.

Autopsy.- This was performed 16 hours after death. The oedema of the upper eyelids on both sides, the proptosis of the eyeballs, and the chemosis of the ocular conjunctivae persisted.

Seen from the inside of the cranial cavity, the wall of the left transverse sinus and the neighbouring dura mater were of normal appearance. On opening the horizontal part of the sinus, one half inch of its wall was of a brownish colour and showed slight roughening of the surface; there was a septic clot attached to the wall, but the lumen was not occluded. In the sigmoid portion of the sinus, changes in the wall were more obvious and the clot was larger; here and as far as the jugular bulb the wall was blackish in colour and was much roughened, while the lumen contained a quantity of semipurulent, septic thrombus.

The thrombus extended forwards along the left inferior petrosal sinus to the cavernous sinus. The left superior petrosal sinus contained a little septic clot only at its two ends - posterior and anterior.

The walls of both the cavernous sinuses were markedly discoloured; there was roughening of the endothelial surface and the lumina contained a large quantity of septic thrombotic material.

The posterior intercavernous sinus was similarly

involved, but the anterior one was healthy except where it joined the right and left cavernous sinuses.

The right superior and inferior petrosal sinuses contained septic material only in their anterior half.

The blood vessels over the surface of the cerebral hemispheres were slightly congested, but no generalised leptomeningitis could be diagnosed by the naked eye. Pus was present in the region of the left lateral cerebral fissure (Sylvian fissure); the pus was in relation to the middle cerebral veins lying in the fissure and was largely, if not entirely, confined to their lumina.

On opening the sphenoidal air sinuses through the basis cranii, the periosteal layer of their mucous membrane was found to be rather congested, but the mucous surface was moist and healthy.

Small multiple abscesses, typical in appearance of general pyaemia, were present in the lungs.

Bacteriology.- From the cavernous venous sinuses and from the pus in the leptomeninges of the left lateral cerebral fissure a growth of haemolytic streptococci and of Bacillus coli was obtained. The pulmonary abscesses gave a pure growth of haemolytic streptococci.

Commentary.

The primary focus of infection was a chronic inflammation of the left middle ear cleft. The disease involved the bone and caused septic thrombosis in the adjacent sigmoid portion of the transverse sinus. From here the thrombotic process advanced not only along the sinus for a short distance but also along the left inferior petrosal sinus and thus reached the cavernous sinus of the same side. From the left cavernous sinus the clot extended into the posterior intercavernous sinus, thus reaching the right cavernous sinus. From the cavernous sinuses, the process extended into the pial veins and gave rise to a leptomeningitis. Micro-organisms having reached the general circulation were carried to the lungs, where they gave rise to small multiple abscesses.

The micro-organism responsible for the condition was a haemolytic streptococcus; the Bacillus coli which was also isolated from the thrombus in the cavernous blood sinuses was undoubtedly a post-mortem invasion.

CASE VI. Suppuration in the Right Posterior Ethmoidal and Sphenoidal Air Sinuses: Orbital Abscess: Cavernous Sinus Thrombosis: Acute Lepto-meningitis: Operation: Death: Autopsy.

This case shows that for the development of cavernous sinus thrombosis it is not necessary for the primary thrombus to occur in a vein at the first site of infection. In the general consideration of the pathways of infection of the intracranial structures by direct extension through the bone (pg.14), it was noted that at any stage of erosion a Haversian canal or the diploë may be opened into. Since red marrow is loose in structure and exceedingly vascular, containing large numbers of blood spaces, it is a good medium for the progressive development of pyogenic infection. The blood from the large amount of diploë in the walls of the higher accessory nasal air cavities drains directly or indirectly into the cavernous blood sinus; therefore, when the marrow becomes infected, there is a potential and ready source of infection of the blood sinus.

That the course of infection beginning by direct extension through loss of continuity in the bone and later continuing by the venous blood stream is a not

infrequent mode by which the cavernous sinus becomes infected is shown by the fact that it occurred in three of the series of thirteen cases (Cases VI.,X., and XI.).

The following are the details of the case and the argument which has led the writer to place it in this category.

M.F., female, aged 26, was admitted to the Eye Department of the Royal Infirmary, Edinburgh, on the evening of 31st December 1921, with a history of neuralgia of the right side of the face, commencing one month previously. This was followed by swelling of the right upper and lower eyelids.

On admission she was examined by Dr H.M. Traquair, whose report was as follows: "The patient, a woman of poor physique, was obviously ill; the temperature was 101°F.; pulse 100. The right eyelids were swollen, occluding the palpebral fissure; the right eyeball was proptosed and the movements restricted; there was slight chemosis of the ocular conjunctiva and great tenderness in the inner upper angle of the right orbit.

"The fingers, employed for testing the vision, were seen, and the peripheral field, as tested by the hand, was not restricted. Both pupils reacted to light, but the movements were sluggish; there was no

swelling of the right disc and the veins were slightly congested."

As the examination strongly suggested the presence not only of an orbital abscess but an intracranial complication, the patient was at once transferred to the Ear and Throat Department, where she was examined by Mr J. D. Lithgow, F.R.C.S.Ed., who evacuated a subperiosteal abscess on the inner wall of the orbit.

On the following day (1st January, 1922) the patient's condition was aggravated and signs of meningitis were now very obvious; the temperature was 102°F.; no cerebrospinal fluid could be obtained on lumbar puncture. The patient gradually became comatose and died on the evening of 2nd January.

Autopsy (limited to the head).- For the following brief record of the post-mortem appearances I am indebted to Dr H. M. Traquair: "A diffuse basal leptomeningitis was present; the longitudinal and lateral blood sinuses contained no ante-mortem clot. No naked-eye changes were observed in the bony walls of the air sinuses. No pus was found in the frontal and maxillary sinuses. After removal of a block of bone containing the ethmoidal and sphenoidal sinuses, pus was seen in the right

posterior ethmoidal cells and sphenoidal cavity, but the corresponding cavities on the left side appeared normal."

In the removal of the block, the lateral incisions in the sagittal plane were made rather close to the middle line, consequently the orbital and ethmoidal areas were partially damaged; this was specially pronounced on the left side.

Preparation of Material for Microscopic Examination.- The whole block removed at autopsy, having been decalcified for several months in Parenny's solution, was divided in the coronal plane by an incision through the middle of the pituitary body. The anterior block contained the posterior ethmoidal cells on both sides and a portion of the left sphenoidal sinus. The posterior block comprised both sphenoidal air sinuses and the cavernous blood sinuses. The right optic nerve was *in situ*. From the anterior block 300, and from the posterior 100 serial sections were made.

Report on the Material examined Microscopically.

(1) The right nasal cavity contained a large amount of pus. The nasal mucosa showed dense cellular infiltration, the cells being mostly of the small

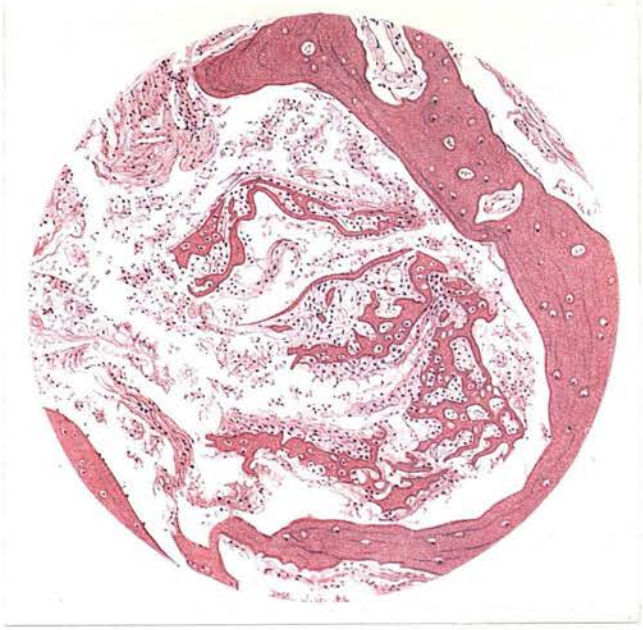


Fig.34.- Right naso-ethmoidal wall. In the centre of the field a detached portion of dead bone is lying in pus; the sequestrum, irregular in outline, has been largely absorbed by osteoclastic action.

Fig.35.- Right orbito-ethmoidal wall. In the centre of the field is a Haversian system: the blood vessels contain fibrinous clot and osteoclasts are eroding the bone (osteoporosis), producing a sinuous outline. On the left of the field is a small detached sequestrum.

To face page 99.

round type, but scattered polymorphonuclear leucocytes were fairly numerous. The mucosa was very vascular, the smaller venules being distended and containing many polymorphonuclear leucocytes. Diapedesis of these cells through the vessel walls was active. The underlying bone showed marked osteoporotic change, and the arteries in the deeper mucosa presented considerable thickening of their walls. Between the periosteal layer of the nasal mucous membrane and the bone were small collections of pus.

(2) Ethmoidal Air-Cells.- The right posterior ethmoidal air spaces contained considerable purulent secretion. The mucous membrane was thickened and in places the lining epithelium had desquamated; the mucosa was oedematous. It was densely infiltrated by cells, many of which were polymorphonuclear leucocytes. The smaller blood vessels were greatly dilated; many polymorphonuclear leucocytes were present in their lumen and diapedesis of these cells was very active. Great osteoclastic activity was taking place in the bony wall of one of the air cells. (Fig.36). In another of the air cells a considerable area of mucosa was necrotic and disintegrating. The bony wall between the ethmoidal cell and the nasal cavity showed considerable osteoporosis, and at onc

Fig.36.- The mucous membrane (a) of a right posterior ethmoidal cell showing inflammation; the lymphatic and blood vessels are dilated and the tissues are densely infiltrated by cells. There is osteoporosis of the bone.

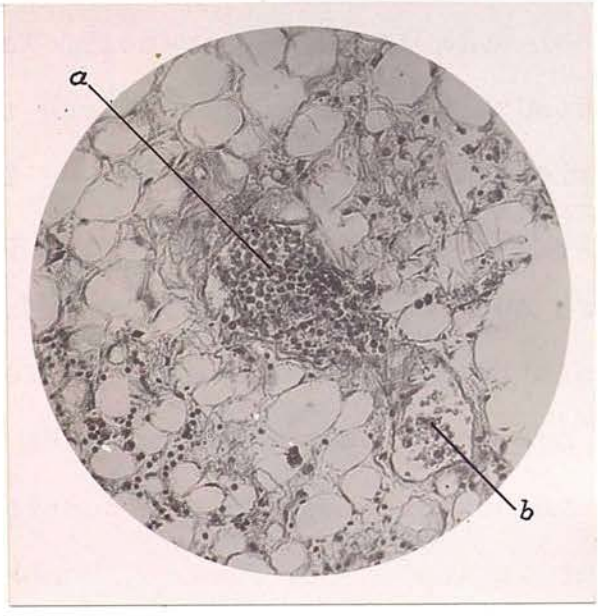


Fig.37.- Fatty tissue in the right orbit: The vein (a) is filled with septic thrombus; vein (b) shows commencing thrombosis. There is diffuse cellular infiltration in the neighbourhood.

To face page 100.

place a small piece of dead bone (sequestrum) was lying free and had very largely disappeared through osteoclastic action (Fig.34).

(3) Orbital Contents (right).- Sections in the coronal plane showed muscle fibres, motor nerves and the optic nerve.

(a) A fragment of bone detached at the autopsy - part of the orbito-ethmoidal wall - showed considerable osteoporosis (Fig.35) especially on its ethmoidal aspect. The fragment contained also a Haversian canal infiltrated by pus.

(b) In the neighbourhood of this area the orbito-ethmoidal wall showed cario-necrosis; the orbital periosteum had been stripped from the bone by pus (subperiosteal orbital abscess). The pus was infiltrating the deeper layers of the periosteum.

(c) Here and there in the orbital fat were a few areas of scattered polymorphonuclear leucocytes, but there was no pus in the ocular muscles and none in or around the branches of the oculoomotor nerve. Pus was present in the pia-arachnoid sheath of the optic nerve. In the orbital connective tissues the small veins were filled with septic thrombi (Fig.37).

(4) Sphenoidal Air-Cells.- The serial sections of this region showed the right sphenoidal sinus

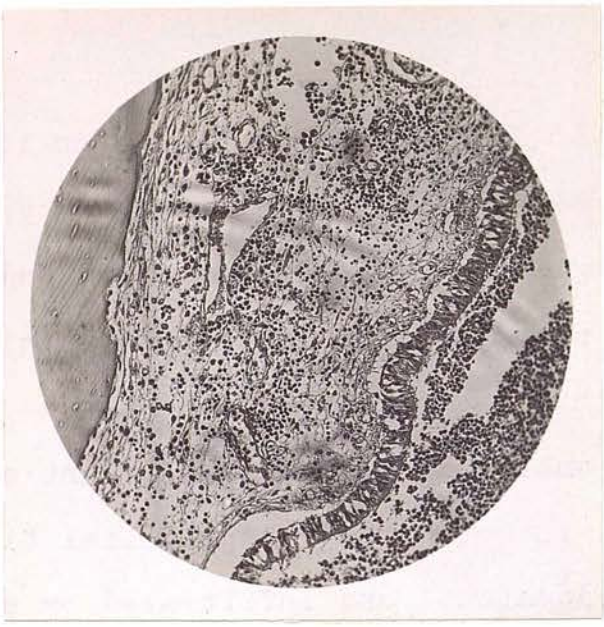


Fig.38.- The mucous membrane of the right sphenoidal sinus shows dilatation of lymphatic and blood vessels, oedema, and cellular infiltration.

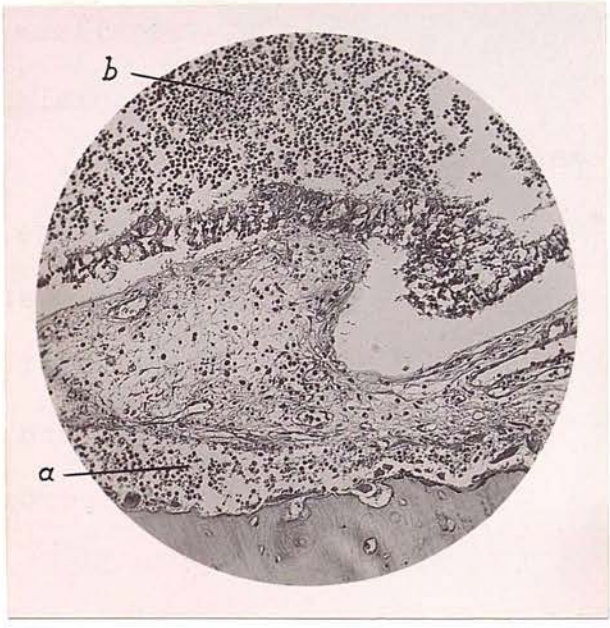


Fig.39.- Subperiosteal abscess (a) in the floor of the right sphenoidal sinus. Pus is present in the sphenoidal cavity (b).

To face page 101.

intact, but the left air cavity had been largely destroyed in removal of the block at autopsy; both Gasserian ganglia were present in part, and the neighbouring nerve bundles of the 5th cranial nerves were seen within the skull.

The columnar epithelium of the right sphenoidal air sinus was intact; the subepithelial tissue was thickened, oedematous, and infiltrated by numerous cells, many of which were polymorphonuclear leucocytes. The smaller blood vessels were greatly dilated, contained numerous polymorphonuclear leucocytes, and diapedesis of these cells through their walls was active (Fig. 38). The cancellous bone in the floor and upper portion of the lateral wall of the air sinus was considerable in amount. There was widespread infection of this diploic tissue, but definite foci of pus were not present. Osteoporosis was occurring in many of the Haversian systems and some of them showed infection. In the bony floor of the sinus was an area in which osteoporosis was very active, and the overlying mucous membrane had been stripped from the bone by pus forming a subperiosteal abscess (Fig. 39).

(5) Cavernous Blood Sinuses.- The blood spaces comprising both cavernous sinuses were completely filled by septic clot, this being infiltrated

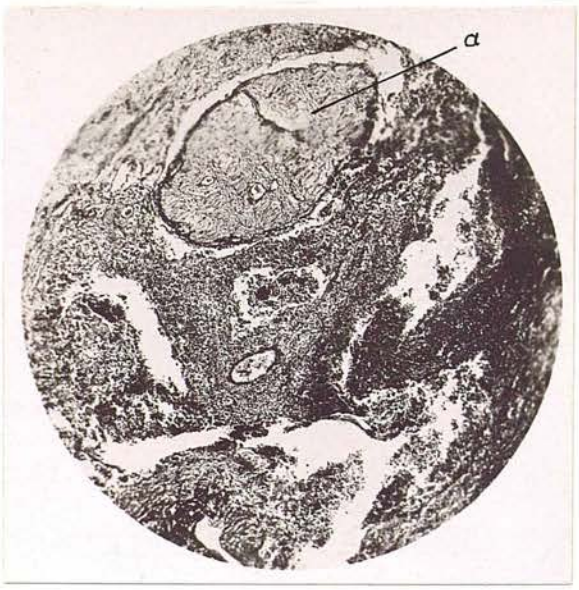


Fig.40.- Right cavernous sinus containing infected thrombus. (Nerve bundle (a) seen in its lateral wall.)

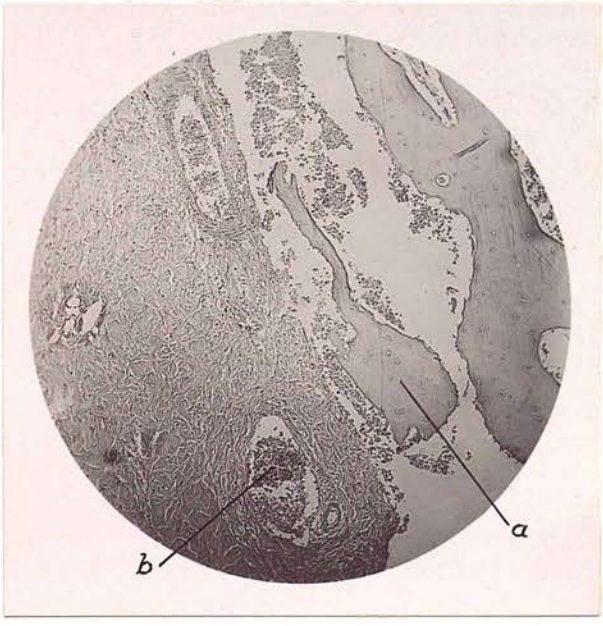


Fig.41.- Small sequestrum (a) in a subperiosteal abscess in relation to the right lateral wall of the sella turcica, with vein of dura mater (b) containing septic thrombus.

To face page 102.

throughout by polymorphonuclear leucocytes (Fig.40). Septic thrombosis had also occurred in the circular sinus.

(6) Carotid Venous Plexus.- On the right side, the carotid plexus was full of pus and the structures outside the muscular coat of the carotid artery had disappeared. The veins of the carotid venous plexus on the left side were filled by septic thrombi.

(7) Meninges and 5th Cranial Nerve.- The pia-arachnoid and connective tissue present in the sections in the neighbourhood of each cavernous sinus, and the loose areolar tissue around the nerve bundles composing the 5th cranial nerve were infiltrated by polymorphonuclear leucocytes and by large and small, round or oval, mononucleated cells. One of the nerve bundles showed polymorphonuclear leucocytes within the perineural sheath and among the nerve fibres. The smaller pial vessels were dilated.

Small veins containing septic thrombi were present in the dura mater of the middle cranial fossa (Fig.41).

The layers of the dura mater forming the walls of the cavernous spaces and those layers round many of the smaller dural blood vessels were infiltrated by cells of inflammatory type.

A collection of pus had stripped the dura mater from the sella turcica and adjacent portion of the middle cranial fossa (subperiosteal abscess).

Sections cut in series showed that this abscess was continuous beneath the periosteum of the right foramen lacerum medium with a similar subperiosteal abscess on the naso-pharyngeal aspect of the basi-sphenoid. Several small detached sequestra were present in the pus (Fig.41).

Sections at the posterior bony angle of the foramen lacerum medium showed the pus of the sub-periosteal abscess communicating with pus in contiguous bone marrow spaces.

The more anterior sections already referred to demonstrated the subperiosteal abscess extending uninterruptedly across the medial plane; in those cut more posteriorly, the pus was burrowing backwards in the form of isolated finger-like extensions.

Bacteriology.- Through the kindness of Professor T. J. Mackie, a number of sections were specially stained to demonstrate the presence of micro-organisms. Gram-positive streptococci were present in the pus in the following situations, namely, the right nasal cavity, a Haversian canal on the right naso-ethmoidal wall, the ethmoidal air cells, and the subperiosteal orbital abscess.

Commentary.

There was old-standing chronic inflammation of the nasal and ethmoidal mucosa on the right side, as shown by the marked osteoporosis of the underlying bone. In the naso-ethmoidal wall the inflammatory process was of such long duration that a small piece of dead bone had actually been separated and had been very largely absorbed by osteoclasts. From information supplied to the writer as to the clinical course of other cases showing suppuration in the naso-ethmoidal area, and from the microscopic appearances in this case, there is no doubt that the suppurative inflammation in the ethmoid had caused destruction of the orbito-ethmoidal osseous wall, and by direct extension produced a subperiosteal abscess on the orbital aspect of the lamina papyracea.

The small amount of pus present in the fatty tissue of the orbit may have been derived from the subperiosteal abscess or from septic thrombi in small branches of the ophthalmic vein. The former possibility is most unlikely, as the periosteum is a membrane very resistant to rupture in cases of subperiosteal abscesses, and secondly, had rupture of the periosteum occurred, the suppuration within the orbital tissues would have been much greater in

amount and more widespread. It seems certain, therefore, that the small scattered foci of pus present in the fatty tissues were secondary to septic thrombosis of the ophthalmic veins. The septic thrombi in the small branches of the ophthalmic veins, present in the series of sections, were very recent, as the infection was found to be confined almost entirely to their lumina (Fig.37).

As will be argued later, the writer is of opinion that the septic thrombosis of the branches of the ophthalmic veins occurred as a result of the septic thrombotic process in the cavernous sinus (retrograde thrombosis).

The mode of origin of the subperiosteal collections of pus around the basisphenoid was similar to that described in connection with the subperiosteal orbital abscess, that is, by direct extension through the bone.

Although the inflammation in the mucosa of the right sphenoidal air sinus was mainly of an acute character, chronic changes of some duration must have been present to account for the considerable osteoporosis found in its bony wall. Again, so the writer is informed, this is in accordance with clinical experience, many cases of sphenoidal air sinus suppuration being associated with inflammation

of the posterior ethmoidal cells.

The infection of the bone marrow was mainly a widespread and diffuse polymorphonuclear leucocytic infiltration. Hence it is concluded that the infection having obtained direct access through the compact bone of the wall from one or more of the air sinuses, had diffused slowly through the diploë. In one or two areas only, the infection was in the form of localised collections of pus; these foci were due undoubtedly to retrograde septic thrombosis of blood spaces in the bone marrow, secondary to the same process in the cavernous sinus. These interpretations are supported by the nature of the changes seen in other cases of the present series, in which infection of the red marrow occurred by extension of the septic thrombosis along the diploic veins draining into the cavernous sinus; in such cases the infection is in the form of localised abscesses and is not a diffuse cellular infiltration.

Route of Infection of the Cavernous Blood Sinus.- As mentioned above, the initial source of the infection in this case was the inflammation in the air sinuses.

The cavernous blood sinus, however, may have been infected from one of three possible foci:

These are (a) the mucous membrane of the sphenoidal or ethmoidal air sinuses; (b) the bony wall of the ethmoidal or sphenoidal air sinuses; (c) the subperiosteal orbital abscess.

(a) The Mucous Membrane of the Air Sinuses.- Infection passing from the mucous membrane to the cavernous blood sinus occurs by the blood stream and, as already stated (pg.27), may arise, firstly, by extension of a septic thrombus along a vein; secondly, by a septic embolus carried along the vein; or thirdly, by the infecting micro-organisms being conveyed by the blood stream and lodging in the meshes of the cavernous sinus. In the present case, no thrombosed vein was found in the mucosa; but even if a septic thrombus had been observed, it is unlikely, from the histological appearances, that a conclusion could have been drawn as to whether it was a primary infection in the mucosa or secondary to the thrombosis of the cavernous blood sinus.

Whether infection of the blood sinus arises from the micro-organism itself lodging in it, and without thrombosis of veins, must be problematical in every case; this question has been discussed already (pg.27).

(b) Bony wall of Ethmoidal or Sphenoidal Air

Sinuses.- In the course of a cario-necrotic process in compact bone, Haversian canals are opened up and extension of the infection may occur along them into the neighbouring red marrow spaces. In the present case this was actually seen in sections of the bony walls of the ethmoidal and sphenoidal cavities, the fine connective tissue of some of the Haversian spaces being infiltrated with polymorphonuclear leucocytes.

(c) The Subperiosteal Orbital Abscess.- In this case, infection of the cavernous blood sinus might have arisen from the subperiosteal orbital abscess; this would have occurred either by thrombosis of the periosteal veins draining into the ophthalmic veins or by extension of the pus from the abscess along the exposed Haversian canals in the medial orbital wall. In the latter case, infection would pass first to the bone marrow and thence to the cavernous sinus. As infection of the red marrow had already occurred during the course of the cario-necrotic process, the question whether the actual thrombosis of the cavernous sinus arose primarily from the infected diploë, or from the subperiosteal abscess by way of the diploë, seems merely one of academic interest. But it is possible that the

determination of this point may have some bearing on the general question of the factors responsible for the spread of the infection from the diploë to the cavernous sinus at a particular moment in the course of the disease.

After considering these three possible foci of infection of the cavernous blood sinus, it seems probable to the writer that, in this case, the blood sinus became infected from the red marrow in the wall of the affected sinuses.

Summary.- Inflammation of the mucosa of the ethmoidal and sphenoidal air sinuses extended to their osseous walls, inducing a chronic cario-necrosis. During the course of the extension of the inflammatory process through these walls, the red marrow became infected. Later, the infection passed by way of diploic veins to the cavernous blood sinus giving rise to acute septic thrombosis. The septic thrombus in the blood sinus then extended along tributary veins into the orbit, dura mater, and pia mater. From the veins of the pia mater an acute purulent leptomeningitis developed.

CASES IN WHICH THE INFECTION OF THE CAVERNOUS BLOOD SINUS WAS RESTRAINED.

CASES VII. to XIII. INCLUSIVE.

CASE VII. Meningococcal Leptomeningitis: Death: Autopsy: Inflammatory Changes in the Sphenoidal Air-Sinuses and Early Cavernous Sinus Thrombosis (Streptococcal): A Case illustrating Double Infection.

This case of infection of the cavernous blood sinus is of especial interest since it is one of double infection. Meningococcus intracellularis, which was obtained in pure culture from the lepto-meninges, was associated with a streptococcal infection of the sphenoidal air-sinuses and a commencing septic thrombosis of the left cavernous blood sinus due, it is believed, to the latter micro-organism.

I.L., female, aged 33, was admitted to the Royal Infirmary, Edinburgh, on 15th April 1922, under the care of Dr Edwin Matthew to whom I am indebted for the following clinical notes. The patient complained of pain and stiffness in the neck. Her husband reported that she had been slightly delirious on one or two occasions during the past week. In January she had had influenza, and since then she had frequently complained of feeling cold. Prior to this her health had been good.

On 8th April, her present illness commenced with an attack of shivering and vomiting. The vomiting continued on the following day. On the 10th, she was very restless and delirious. On the 11th, pain was complained of at the back of the neck. At the same time she suffered from hallucinations.

When examined on the 15th April, the neck was rigid and there was great pain when passive movement was attempted; the head was not retracted; the pupils were equal; the knee-jerks were exaggerated; there was no ankle clonus; doubtful Kernig sign was elicited. The pulse was slow and full; temperature 101°F.

No ophthalmoscopic changes were observed; no middle-ear disease was present. Anterior rhinoscopic examination of the patient in bed revealed nothing of importance.

The cerebrospinal fluid, which was not under undue pressure, showed some opalescence. When centrifuged it contained a few lymphocytes and polymorphonuclear leucocytes, and one or two red cells; no micro-organisms were found in films or on culture.

The patient continued restless and irritable, and on the 21st had incontinence of faeces; the exaggerated knee-jerks had disappeared; there was no

clonus, and plantar reflex was normal. A temporary external squint of the right eye had developed.

On 29th April, the cerebrospinal fluid was opaque , but still not under undue pressure; the polymorphonuclear leucocytes were now more numerous, but no micro-organisms of any kind were obtained. During the whole of the time the patient was in hospital the temperature was elevated.

On 30th April, the patient died suddenly.

A provisional diagnosis was made of epidemic cerebrospinal meningitis or tuberculous meningitis.

Autopsy.- There was acute, purulent, basal meningitis with a scanty greenish exudate, most marked in the cisterna pontis and on the under surface of the cerebellum. The superior longitudinal and lateral blood sinuses were normal.

Macroscopically, both middle ears and mastoid cells showed no pathological changes. The nasal air-sinuses which were opened at the sectio were healthy, with the exception of the sphenoidal air cavities, which contained greenish pus.

In the internal organs the only changes of a pathological nature were observed in the spleen. This was fully twice the average size and of soft consistency.

A block of bone was removed from the floor of the middle cranial fossa. This comprised the superior wall or roof, with a portion of the lateral walls of both sphenoidal air sinuses and the upper part of the intersinus septum attached to it; the two cavernous blood sinuses, with the intercommunicating circular sinuses, the internal carotid artery, and the cranial nerves contained in the lateral wall of the cavernous sinuses. The bone was decalcified in Parenny's solution.

Report on the Material examined Microscopically.

The Mucous Membrane of the Sphenoidal Air Sinuses.- The mucous membrane lining the cavities was thickened and oedematous. The blood vessels were dilated and, through the walls of some of them, active diapedesis of polymorphonuclear leucocytes was taking place. Small petechial haemorrhages were present in the mucosa. The sub-epithelial tissue was densely infiltrated by large and small round mononucleated cells, plasma cells, and polymorphonuclear leucocytes, the small round mononucleated cells being predominant. The condition, therefore, was one of early acute inflammation, superimposed on subacute and chronic changes.

The Osseous Wall of the Sphenoidal Air Sinuses.- On the mucosal surface of the bony roof of the air sinuses, a considerable amount of osteoclastic activity was taking place. In a number of areas, large multinucleated osteoclasts had absorbed the bone with the formation of "bays" in which they were lying. In some instances this was observed within the openings of Haversian canals, and even deep in the bone.

On the cranial aspect of the bony roof, similar activity was present and more pronounced. The osteoporotic changes were the result of stimulation by long-standing absorption of toxins derived from the micro-organisms responsible for the chronic inflammatory changes in the sphenoidal air sinus.

The Bone Marrow.- The red marrow in the medial portion of the roof of each sphenoidal sinus was very cellular, but the cells were of normal type, there being no excess of polymorphonuclear leucocytes. The marrow cells, however, had proliferated and commenced to invade the connective tissue spaces of those Haversian canals which were continuous with the diploic space. In a number of the red marrow spaces situated at the junction of the roof and lateral wall of the right sphenoidal sinus, acute

osteomyelitis was present, polymorphonuclear leucocytes being numerous. Many of the Haversian canals in this neighbourhood were invaded by polymorphonuclear leucocytes, and here and there active diapedesis of these cells was occurring through the walls of the smaller blood vessels.

The Leptomeninges.- In some of the sections of the series the pia-arachnoid membrane was seen as it lay in relation to the nerve bundles in the lateral wall of the cavernous blood sinuses on its superior or cerebral surface. The meshes of the membrane were densely infiltrated with polymorphonuclear leucocytes and large and small mononucleated cells. Through the walls of the small pial vessels, active diapedesis of the first type of cell was taking place. In some places the pus had broken through the perineural sheath of a nerve bundle and was infiltrating between the nerve fibres.

The Cavernous Blood Sinuses.- Pus was present in some of the large blood spaces forming the left cavernous sinus. Only one space, however, was filled completely with septic clot; in the remainder the clot was comparatively small. On the other hand, the blood spaces of the right sinus showed no septic thrombosis. The dura mater forming the

lateral wall of the left cavernous sinus was in many places infiltrated by polymorphonuclear leucocytes, the infiltration being most marked immediately beneath the endothelial lining of the blood sinus.

Bacteriology.- Films from the meningeal pus taken at the post-mortem and examined by Dr W.R. Logan showed Gram-negative diplococci, many of which were within polymorphonuclear leucocytes. Cultures of the pus yielded a pure growth of Meningococcus intracellularis (Weichselbaum). A culture from the pus in the sphenoidal air-sinus gave a growth of a streptococcus occurring in pairs, possibly a pneumococcus.

Professor T.J. Mackie has studied the bacteriology of the case in certain sections supplied to him from the series. Numerous short chains of Gram-positive streptococci were present in the septic clot which filled completely one of the cavernous blood spaces on the left side; in the blood spaces showing commencing clotting, micro-organisms were not demonstrable. Similar streptococci were found in the pia mater in relation to the wall of the blood space containing the septic clot, and also in the fatty tissue round the maxillary division of the left 5th cranial nerve. In the fatty tissue, a chain of micrococci

composed of four elements was seen within a mono-nucleated cell.

Short chains of Gram-positive micrococci were present in the layers of the mucous membrane of the left sphenoidal air sinus, but were not demonstrated in the adjacent diploë. This is in accordance with the cytological examination, there being no acute inflammatory changes in the bony wall at this site.

As already noted, in the anterior sections of the series acute osteomyelitis was present in the red marrow spaces situated at the junction of the roof and lateral wall of the right sphenoidal sinus. In the more posterior sections of the series, however, from which specimens were taken to demonstrate micro-organisms, the red marrow area was absent, there being only compact bone.

As would be expected from the cytological examination of the red marrow in the medial portion of the roof (pg.115), no micro-organisms were found in the sections stained for bacteria. Gram-negative meningococci were not demonstrated in the lepto-meninges round the cavernous sinus. This will be readily understood as only a few small portions of pia mater were present in the sections stained for micro-organisms.

Conclusions.- It has been shown by numerous investigators that in some cases of meningococcal "carriers" the micro-organism may have its habitat not only in the nasopharynx but also in the ethmoidal and sphenoidal air cavities. In considering the etiology in the present case, it is immaterial whether the patient was or was not a carrier of the Meningococcus, since it is certain that this micro-organism had only recently invaded the body tissues; according to the present generally accepted teaching, it was carried by the blood stream to the leptomeninges, in which it settled.

The early acute inflammatory changes in the mucous membrane of the sphenoidal sinus were due to a lighting up of the pre-existing chronic inflammation; the acute changes were caused by a streptococcus, as demonstrated in the sections, and the chronic changes, in all probability, were caused by the same micro-organism. The acute changes in the air sinus were later in onset than the meningitis, and it would seem probable that the meningeal inflammation had some ill-defined etiological relationship to the onset of the later acute changes in the air cavity. It is certain that in this patient there was a double infection; while the changes in the sphenoidal sinus mucosa were

due to streptococcus, the acute leptomeningitis was caused by the Meningococcus intracellularis.

Three cases described by D. Embleton and E.A. Peters showed acute osteomyelitis in the bony wall of the sphenoidal sinus, and they state that in two of these the Meningococcus was present in the inflamed diploë.

Notwithstanding this observation the writer believes, from general knowledge of the pathogenic effects of Meningococcus intracellularis, that in the majority of cases in which another pyogenic micro-organism is present in pus in the air sinus, the osteomyelitis is due to invasion of the bone by the latter micro-organism. He believes that, in the present case, the acute osteomyelitis was due to the streptococcus and that it passed from the sphenoidal mucous membrane along the Haversian spaces to the diploë of the osseous wall and thence to the cavernous blood sinus.

In previous cases of the series the acute osteomyelitis present was shown to be due to retrograde thrombosis along the diploic veins from the infected cavernous sinus. But in the present case, since the thrombosis in the cavernous blood sinus was very recent (vide infra), and since none of the venous

tributaries in the series of sections were thrombosed, the acute osteomyelitis had not arisen secondary to the cavernous sinus infection.

The conclusion that the thrombosis in the cavernous sinus was recent is based on the facts that complete thrombosis was limited to one of the blood spaces on the left side, and that extension into other blood spaces on this side was only commencing. It is known that, in the majority of cases, when septic thrombosis occurs in one of the blood spaces of a cavernous sinus, its extension into the other spaces of the same sinus and into those of the opposite side is rapid.

The absence of the clinical signs of cavernous sinus thrombosis is explained by the microscopic examination of the sections; the majority of the blood spaces being still patent permitted of the continuance of the venous circulation (pg. 34).

The acute changes due to the streptococcus developed late in the course of the meningococcal meningitis. This circumstance is in accordance with the clinical and bacteriological observations of J. Fitzgerald. In two cases recorded by him, examination of the cerebrospinal fluid during the course of the disease showed a terminal and fatal infection

of the leptomeninges by the pneumococcus. Similar cases have been recorded by Netter and Salanier, Barbier and Lebée, and others.

The investigation of this case raises a further interesting and very important point in relation to the infection of the leptomeninges by the meningococcus. In epidemic cerebrospinal meningitis, the question arises whether a chronic change in the mucous membrane of the upper respiratory passages constitutes a factor predisposing the individual to the invasion of his tissues by the meningococcus. The recent work of Lowndes Yates upon the condition of the nasal sinuses in cases of encephalitis lethargica is probably of great importance in solving this problem. He has demonstrated that a number of these cases are associated with an increased power of absorption through the nasal mucous membrane or that of the posterior nasal sinuses, this being due to ciliary paralysis and paralysis of mucous secretion. He asserts that the paralyses "are produced either as a result of chronic rhinitis or from a single heavy infection of the nasal mucous membrane, of the type known colloquially as influenza."

CASE VIII. Chronic Bilateral Middle-Ear Suppuration: Bilateral Radical Mastoid Operation Ten Years previously: Septic Thrombosis of the Sigmoid Portion of the Right Transverse Sinus, Inferior Petrosal Sinus, and Both Cavernous Sinuses: Death: Autopsy.

Although the clinical history of the intracranial affection is deficient in the present case, it is included in the Series since the spread of infection, as demonstrated at autopsy, is typical of cases in which the infection of the cavernous blood sinus arises from chronic middle ear disease. Whereas the blood infection in Case V. was of the fulminating type, in the present Case VIII. it was restrained. Allowing that the thrombotic process began in the transverse sinus four days before the patient was admitted to hospital, the course of the disease was fifteen days.

J. K., male. aged 15.

In 1919, the patient was admitted to the Ear and Throat Department, Royal Infirmary, Edinburgh, under the charge of Dr J. S. Fraser, who performed a bilateral radical mastoid operation.

In 1925, the patient reported at hospital. The

mastoid cavities were very dirty, containing newspaper packing and wax.

In 1928, the patient again reporting, much desquamation and many granulations were found in the mastoid cavities. Under treatment, the condition improved. In November of this year, radiograms showed the paranasal sinuses to be clear.

On 27th May 1929, the patient was sent to the Royal Infirmary as a case of appendicitis and was admitted to one of the general Surgical Wards. His doctor reported that for the past few days the boy had suffered from headache and had had a temperature as high as 104°F. On the day before admission, he began to vomit and there was pain and tenderness over the abdomen.

On admission, the patient complained of pain in the lower part of the abdomen on the right side and of headache. The tongue was dry and furred and on palpating the abdomen there was distinct resistance in the right iliac fossa. An appendectomy was performed and to the naked-eye the viscus appeared inflamed.

On 29th May, the temperature having remained high, the patient was seen by Dr J. S. Fraser. The left mastoid cavity was healthy, but the right

Case VIII.

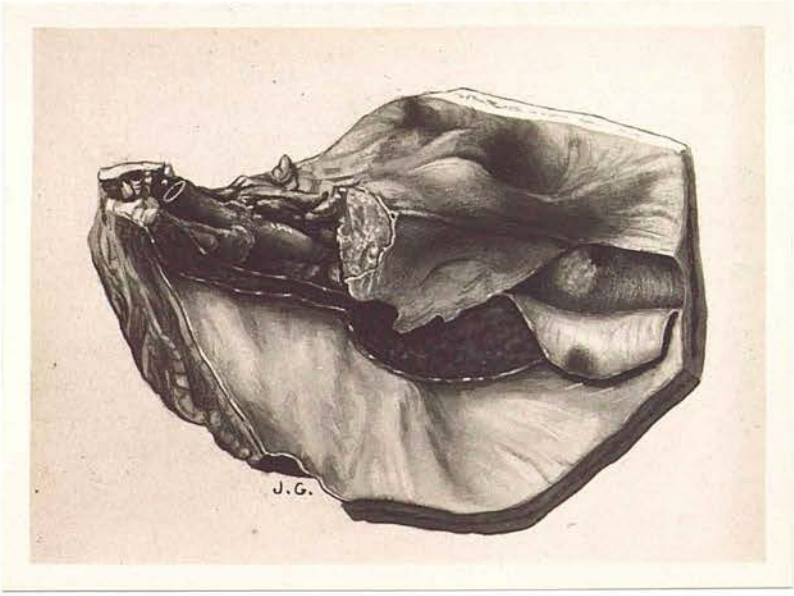


Fig.42.- Photograph of a drawing showing the carious area and adjacent sclerosed portion in the bony groove of the sigmoid portion of the right transverse sinus. The dural wall of the sinus corresponding to the diseased bone is discoloured and the transverse sinus contains a thrombus which has extended along the inferior petrosal sinus. The apex of the petrous part of the temporal bone has been removed to expose the carotid canal.

To face page 125.

contained some granulations. A certain amount of stiffness of the neck was present and a positive Kernig's sign was elicited. No pus was seen in the nose.

Lumbar puncture yielded clear cerebrospinal fluid. This was not examined until nearly twenty-four hours afterwards; then no cells were found in direct films and culture of the fluid did not yield any growth.

On 2nd June, the signs of bilateral cavernous sinus thrombosis had developed, the eyelids on both sides being oedematous and both eyeballs proptosed.

On 5th June, the patient died.

Autopsy.- The right antral cavity contained septic material such as is frequently found in the mastoid after the radical operation, if left untreated by the patient. A probe detected an area of soft roughened bone in the posterior medial angle of the tympanic antrum.

The right transverse sinus contained foul-smelling thrombus which had liquefied in places forming pus. The wall of the sigmoid portion of the sinus at the superior genu was discoloured, and on stripping it from the bony groove, the medial aspect of the small bony area above described was

displayed. The bone immediately around this carious area was discoloured and soft and adjacent to it was a rounded portion of sclerosis, about half a centimeter in diameter, the bone being dense and white.

The right inferior petrosal sinus contained septic clot throughout its whole extent, but no clot was present in the right superior petrosal sinus.

Both cavernous sinuses were filled with septic clot which was liquefying to form pus; this was specially noticeable on the right side. The clot reached the anterior opening of the left inferior petrosal sinus, but did not extend along it nor along the left superior petrosal sinus.

The carotid canal was opened, but no macroscopic sign of infection of the arterial wall was found.

The sphenoidal and ethmoidal air sinuses were healthy.

The internal organs showed the usual signs of toxaemia, but no pyaemic abscesses were present.

Bacteriology.- Direct films of the contents of the right transverse sinus showed Gram-negative bacilli, Gram-positive filamentous forms, and Gram-positive cocci occurring in pairs and short chains, A culture yielded a growth of Bacillus proteus and a streptococcus.

Commentary.

Owing to the patient persistently neglecting to treat the ears after a bilateral radical operation for the cure of chronic otitis media, infection of the mastoid cavities recurred. Extension of the infection into the bone took place on the right side and slowly progressed, causing in one area cario-necrosis with sclerosis in an adjacent portion. The cario-necrotic process led to infection of the contiguous wall of the right transverse blood sinus and a septic thrombus formed within the lumen, This spread along the right inferior petrosal sinus to the right cavernous sinus and thence by the inter-cavernous blood vessels to the left cavernous sinus.

The whole progress of the infection was slow and it reached the blood stream in the transverse sinus probably fifteen days before death occurred.

CASE IX. Furuncle of the Right Nasal Vestibule: Septic Thrombosis of the Cavernous Blood Sinuses: Orbital and Pharyngeal Abscesses: Leptomeningitis: Pyaemia: Death: Autopsy.

In this case, as in Cases I and II, the initial source of infection of the cavernous blood sinus was a furuncle. In the first two cases of the Series, however, the infection was fulminating in type, whereas in the present instance it was restrained. As a result, infection of the dural blood sinus occurred later and the whole course of the disease was more prolonged than in Cases I and II.

Among the features of especial interest in this case is the formation of an abscess of considerable size in the orbit on the affected side and of a large pharyngeal abscess which developed shortly before death. Further, at no period in the course of the illness were there any clinical manifestations of thrombosis in the cavernous sinus of the opposite side, although at the time of death the cavernous blood spaces on both sides were full of pus.

M. W., female, aged 41, was admitted to the Edinburgh City Fever Hospital on 29th October, 1926,

as a case of facial erysipelas. The patient stated that about three weeks previously a painful swelling formed within the right nostril and that the tip of the nose became red and swollen. Later, the inflammation spread upwards and the eyelids on the right side became oedematous. A diagnosis of facial erysipelas was made, the patient being sent to Hospital.

On admission to the City Fever Hospital, however, it was evident to the Medical Superintendent, Dr W. T. Benson, that a more serious condition was present. In addition to the pronounced oedema of the eyelids, the movements of the right eyeball were restricted and there was distinct proptosis of the right eye, associated with chemosis of the ocular conjunctiva.

On 30th October, the eyes were examined by Dr J. V. Paterson. In addition to the changes above described, he found the right pupil fixed and moderately dilated; the retinal veins were thrombosed and the sight in the right eye had disappeared, but light could still be distinguished from darkness. The left eyelids, left eyeball and left optic disc were normal. The diagnosis of septic thrombosis of the right cavernous sinus was made.

On 31st October, an examination of the patient

was made by Dr W. T. Gardiner who corroborated the diagnosis and advised the patient's removal to the Ear, Nose and Throat Department of the Royal Infirmary, Edinburgh. This was done on 2nd November.

On 2nd November, when examined at 5 p.m., the temperature was 100·6°F. and the pulse rate 104. The patient's mental condition was good and she was able to answer questions readily. She did not complain of headache. A slight difficulty was experienced in flexing the chin upon the chest and the movement produced slight pain; Kernig's sign was not elicited and the plantar reflex was flexion; the knee jerks were feeble but equal on the two sides.

The right upper and lower eyelids were markedly oedematous, the condition being more marked in the lower lid, and the palpebral fissure was occluded. The oedema of the upper lid, however, did not prevent the introduction of the little finger beneath the supra-orbital margin and the oedema did not extend on to the forehead; no frontal tenderness was elicited. Proptosis was present, but without downward and lateral displacement of the eyeball. Chemosis of the conjunctiva was pronounced, especially of the ocular layer and on the lateral half of the eyeball. The right pupil, moderately dilated, remained immobile

and the patient could still distinguish light and darkness. The left eyelids, the left eyeball and vision in the left eye were normal.

On nasal examination, the furuncle in the right nasal vestibule previously complained of was no longer present. No pus could be seen in the nasal cavities on either anterior or posterior rhinoscopy. A skiagram of the nasal accessory sinuses could not be made. No swelling was present in the pharynx and the ears were normal.

Proof puncture of the right antrum gave a negative result. Dr W. T. Gardiner considered it advisable, in the absence of any sign of furuncle, to open the ethmoidal and sphenoidal air sinuses by intranasal operation. No pus was found and a swab from the sphenoidal sinus taken at the operation gave no growth later of micro-organisms.

On the following morning, 3rd November, the patient's condition remained much the same, but the temperature had fallen to 98·6°F. and the pulse rate was 96.

On 4th November, the temperature was 101°F; the right lower eyelid was more oedematous and tense and the tissues of the right cheek were swollen. A free incision was made through the eyelid and pus was

evacuated from the orbital fat below the eyeball; the abscess was drained.

On 6th November, the patient became very drowsy and left hemiplegia developed. The temperature continued elevated. A lumbar puncture was performed; the cerebrospinal fluid was under increased pressure and turbid; pus cells were present; a cell count gave 58 per c.mm., of which 85 per cent. were polymorphonuclear leucocytes; globulin was increased in amount; the total nitrogen content was 140 mgm. per cent.; chlorides were 666 mgm. per cent.; no microorganisms were seen in films, but on culture, Staphylococcus aureus, S.citreus, and S.albus were later obtained. A blood culture was made and sixty hours later a pure culture of Staphylococcus aureus had grown.

On 8th November, the drowsiness had passed into coma. The left eyelids and eyeball remained normal.

On 9th November, the patient died.

Autopsy.- A purulent exudate was present in the pia-arachnoid meshes over the base of the brain in the middle and posterior cranial fossae. The pial blood vessels in the anterior fossa and of the lateral and medial surfaces of the hemispheres were congested, but there was no pus in the leptomeninges.

A recent blood clot was situated on the right side of the medulla and a collection of pus was present in this neighbourhood. The left transverse sinus contained pus from the jugular bulb to the torcular, and septic clot was present in the left inferior petrosal sinus; the left superior petrosal sinus was empty.

The anterior part of the right orbital cavity was completely disorganised by purulent infiltration and pus was present in the interior of the eyeball.

An abscess was present on the right lateral and posterior aspect of the pharynx.

At the base of the upper lobe of the right lung were two small abscess cavities, each about 1 cm. in diameter; both lungs were congested and oedematous. small pin-point abscesses were present in both kidneys and a septic infarct was situated in the left renal cortex.

Swabs taken from the pus in the leptomeninges of the base of the brain and from the pus in the left transverse sinus gave a pure culture of Staphylococcus aureus.

Preparation of Material for Microscopic Examination.- As in the previous cases, a large block was removed from the base of the skull and decalcified in Parenny's solution. It was then divided in the

coronal plane into pieces suitable for embedding in paraffin.

Report on the Material examined Microscopically.

1. The Cavernous Blood Sinuses.- Both cavernous sinuses were full of pus throughout their whole extent.

Over a wide area, polyporphonuclear leucocytes were densely infiltrating the layers of dura mater contiguous to the blood spaces and were present in the loose areolar tissue adjacent to the blood spaces. The small dural veins in the neighbourhood of the cavernous blood spaces were dilated.

Although there was pus in the layers of dura mater around the nerves in the lateral wall of the sinus, it had not infiltrated the nerve bundles.

2. The Pituitary Body.- An abscess was present in the upper part of the pituitary body on the right side.

3. The Leptomeninges.- Purulent leptomeningitis existed in those portions of the pia-arachnoid membrane examined in the sections.

4. Body of the Sphenoid Bone.- The body of the sphenoid bone showed considerable purulent osteomyelitis, especially pronounced in that part lying

posterior to the plane of the sphenoidal air cavities. Large portions of the diploë were necrosed and numerous abscesses, some of considerable size, were found. Abscesses existed beneath the periosteal layer of the dura mater covering the superior and lateral surfaces of the body of the sphenoid bone.

The inflammatory changes in the diploë in the region of the air cavities were less pronounced than in the bone lying more posteriorly.

5. The Sphenoidal Air Cavities.- The cavity on the right side, which had been operated upon, contained blood clot. On its upper and lateral wall, thickening of the mucosa due to haemorrhages and oedema was present. The lumen of the left cavity, the one not previously interfered with, contained a small quantity of mucus. The epithelial lining was intact, the veins were dilated, and portions of the subepithelial tissue were oedematous.

6. The Pterygoid Region.- In the soft tissues constituting the pterygoid region on the right side large abscesses were present, and pus was infiltrating the fatty, fibrous, and muscular tissues of the area. The larger veins of the pterygoid venous plexus had disappeared, many of the smaller thrombosed veins persisting.

The microscopic examination of this area was in keeping, therefore, with the existence of the lateral pharyngeal abscess.

On the left side no thrombosed veins and collections of pus were found, but the soft tissues were diffusely but sparsely infiltrated by polymorphonuclear leucocytes and round mononucleated cells.

7. The Carotid Venous Plexus.- The veins of the carotid venous plexus accompanying the internal carotid artery as it traversed the cavernous sinus were not thrombosed on either side.

8. The Orbits.- Sections from these cavities were made near the apex. In the right orbit two small abscesses were present in the fat and muscle in the site of the superior and inferior ophthalmic veins. The walls of these veins were no longer recognisable. In the lateral part of the left orbit towards its apex there was a small area of polymorphonuclear infiltration around a small vein. A second similar area was also present near the lateral orbital wall. The veins were not thrombosed.

In both orbits pus was seen in the pial sheaths of the optic nerves.

9. The Ethmoidal Cells.- The examination of portions of the right ethmoidal labyrinth removed at

the operation performed immediately after admission to the Ear and Throat Department showed no acute or chronic changes either in the mucous membrane or bony walls of these air cavities. What remained of the ethmoidal mucous membrane at autopsy was oedematous and showed haemorrhages due to trauma.

In the left ethmoidal cells which had not been operated upon the mucous membrane was slightly oedematous, the columnar epithelial lining was intact, and some mucopus was present in the lumen of the cells.

Commentary.

Although the clinical signs of septic thrombosis of the cavernous sinus were not recognised until nearly three weeks after the incidence of the furuncle, the cutaneous inflammatory condition had been slowly extending from the right nostril during that period. When the patient was admitted to hospital, the thrombosis of the blood sinus was well established. Both from clinical observation of the nasal cavities at the operation and from subsequent microscopical examination of the tissues, the higher air sinuses can be excluded as the primary source of the infection.

Further, the bacteriology of the case supports

the conclusion that the furuncle was the initial focus. Staphylococci were obtained on culture from the cerebrospinal fluid and blood during life and from the leptomeninges and transverse sinus at autopsy.

As argued in previous cases, e.g. Cases I and II, the route of infection of the cavernous sinus was probably along tributaries of the facial-ophthalmic anastomosis, but thrombosis of the cavernous sinus by selective action (pg.52) must not be altogether disregarded. The infection was restrained and consequently the whole course of the disease was prolonged.

After infection of the right cavernous sinus had been established, the septic thrombotic process proceeded along the various afferent and efferent veins. Thus there arose septic thrombosis of the left cavernous sinus and of the left inferior petrosal and transverse sinuses; thrombosis of diploic veins produced osteomyelitis in the body of the sphenoid bone, and thrombosis of the pial veins gave rise to purulent leptomeningitis. Extension along the emissary veins of the foramen ovale to the pterygoid venous plexus caused septic infection with abscess formation in the pharynx. Finally, the micro-organisms having reached the circulating blood stream gave rise to a general

pyaemia.

In this case, it is a matter of opinion whether the thrombosis of the right ophthalmic veins was primary or secondary to the thrombosis of the right cavernous sinus.

In either event it is a fact that the ophthalmic system on the right side became thrombosed comparatively early in the progress of the infection. The significance of the ocular phenomena was not recognised until the patient was admitted to hospital eleven days before death. On the day following admission, an ophthalmoscopic examination of the fundi oculorum showed that the retinal veins of the right eye were thrombosed, whereas on the left side the veins were normal. Much the same condition existed up to the time of death since microscopical examination of the left orbit showed that the veins even at that time were not thrombosed.

Intimately associated with the condition of the ophthalmic venous system is the remarkable fact that although at the time of death the cavernous blood sinuses on both sides were full of pus and microscopical examination of them and of the surrounding tissue gave a picture to all intents and purposes absolutely similar on the two sides, the patient

never developed clinical signs of thrombosis of the left cavernous sinus and its afferent ophthalmic veins.

The explanation of the absence of clinical signs of the thrombosis on the left side is to be found in the fact that after the left cavernous sinus became thrombosed the thrombotic process did not pass forward into the ophthalmic venous system. From the whole nature of the disease in this case, the thrombus in the left cavernous sinus probably occurred comparatively slowly and hence the collateral circulation of the ophthalmic system of veins - facial-angular and pterygoid - was able to compensate for the progressive obstruction and ultimate cessation of the flow of blood backwards through the cavernous sinus.

It is of very considerable interest in this case that whereas on the left side the thrombus in the cavernous sinus spread backwards along the inferior petrosal sinus into the transverse sinus and jugular bulb and thence as far as the torcular, no similar backward extension occurred on the right side. No precise reason for this phenomenon can be given.

CASE X. Acute Suppuration in the Right Frontal and Ethmoidal Air Sinuses: Orbital Abscess: Osteomyelitis of the Frontal Bone (post-operative): Infective Thrombosis of the Cavernous Blood Sinuses: Acute Leptomeningitis: Death: Autopsy.

As the present case was in its main clinical features very similar to certain other cases of accessory sinus suppuration with intracranial complications in which a complete microscopic examination of the infected tissues was made, the minute examination has been confined to the frontal bone and its coverings in order to investigate the microscopic changes present in acute diffuse osteomyelitis. In this instance the osteomyelitis was consecutive to the operation on the right frontal sinus.

J.W.W., boy, aged 14, was admitted on 1st March 1927 to the Ear and Throat Department, Royal Infirmary, Edinburgh, under the charge of Mr J. D. Lithgow, F.R.C.S.E., to whom I am indebted for the following clinical notes.

The patient complained of pain in the right eye of five days' duration, complicating a cold in the head.

On 1st March, when admitted, swelling of the right upper lid was observed. He had discharge from the right side of the nose and the pain in the eye persisted.

Rhinoscopic examination showed considerable deviation of the septum to the right, profuse muco-purulent discharge and oedematous mucous membrane in the form of small polypi lateral to the right middle concha.

The right upper eyelid was oedematous and tenderness was elicited over the right frontal sinus, especially on pressure upon its inferior wall.

The nasal cavity was packed with cocaine, and inhalations of menthol and the head light were prescribed.

As the pain was very acute in the evening, the right ethmoidal cells and the right sphenoidal sinus were opened. Probes were passed into the frontal sinus and the right antrum, which contained pus, was opened through the nasal cavity.

During the two following days the ocular pain was severe.

4th March. Both right eyelids were now very much swollen; there was also proptosis of the eyeball and pain extended over the right side of the

head. Kernig's sign was present, being more pronounced on the right side.

The right frontal sinus was opened through an eyebrow incision carried medial to the inner canthus. On raising the orbital periosteum along the medial wall, a considerable quantity of pus escaped from the back of the orbit. The frontal sinus was opened and found to contain pus and oedematous mucous membrane. A large area of bone was removed from the anterior wall and an opening made into the nose, through which a drainage tube was passed. A drain was inserted at each end of the orbital incision.

During the three following days the patient's general condition improved and the pain disappeared.

8th March.- A slight parotid swelling had now formed on the right side and an enlarged, tender lymph node was present on the same side of the neck.

10th March.- A spreading cellulitis had commenced on the right side of the neck, and on the 12th had reached as far as the clavicle. The frontal sinus wound was discharging freely, but the oedema of the eyelids was much less.

15th March.- The cellulitis had now almost disappeared.

16th March.- The patient again complained of

pain in the head.

17th March.- Discharge from the frontal wound was considerable; the neck was now normal. The patient was alternately drowsy and excited. The abdominal reflexes were absent; extensor reflexes were weak; a slight Kernig's sign was present, but no stiffness of the neck. Both fundi oculorum were normal.

Lumbar puncture revealed clear cerebrospinal fluid which was not under increased pressure. Professor Edwin Bramwell, who saw the patient on this date, could give no definite opinion as to the presence of cerebral abscess.

An hour after the withdrawal of the cerebrospinal fluid (20 cc.) the patient developed a tetanic spasm followed by clonic movements; breathing became sterterous and the patient cyanosed. These symptoms lasted intermittently for four hours, the patient dying at 5.45 p.m. on the 17th March.

Two hours before death he developed a right-sided paralysis with paralysis of the right side of the face.

Autopsy.- The autopsy, carried out on the following day, was limited to examination of the head. The oedema of the right eyelids and proptosis of the

eyeball were still present. On reflecting the scalp from the right side of the skull, pus was found in the temporal fossa and also invading the temporal muscle. The frontal bone forming the osseous boundary of the fossa was inflamed (osteomyelitis), evidently an extension of the inflammation from the area of the frontal sinus previously operated upon. A wedge of this bone along with the underlying dura mater and the subjacent orbital plate of the frontal bone was removed for decalcification and microscopic examination.

The dura mater in the right middle fossa was very congested and was haemorrhagic.

The leptomeninges were congested. A large patch of purulent exudate was lying in the meninges over the right hemisphere and on the anterior pole of the temporal lobe; the pus had spread on to the adjacent part of the frontal lobe on either side of the lateral cerebral fissure (fissure of Sylvius). The leptomeningitis was localised to this area. There was no evidence of pus elsewhere in the meninges.

On section, the cerebral hemispheres and the cerebellum were oedematous; no abscess was found.

No pus was present in the transverse blood sinuses: pus was present in both cavernous sinuses

and extended into the inferior petrosal sinuses.

The right middle ear cleft was normal.

Macroscopically, the sphenoidal air sinuses were healthy.

There was pus in the right orbit, behind the eyeball.

Bacteriology.- Streptococcci in direct film and on culture were obtained from the pus in the meninges.

Report on the Material examined Microscopically.

1. Portion of the Frontal Bone lateral to the Right Frontal Sinus with attached part of the Orbital Plate.- This was taken, as already stated, in order to demonstrate the inflammatory changes in the diploë (osteomyelitis). In this region the inflammation in the bone was secondary to the operation on the frontal sinus: this conclusion is based on the clinical history and the macroscopical appearances observed during life and at the post-mortem.

Some of the diploic spaces showed no change; the cells were of the ordinary type and comparatively sparsely distributed through the areolar tissue. In others again, the cellular distribution was denser and many of the cells were polymorphonuclear leucocytes which showed more or less complete structural

differentiation. In other areas of the diploë the ground substance had undergone a gelatinous change. Finally, some of the diploic spaces were very cellular owing to the presence of numerous polymorphonuclear leucocytes, while the small blood vessels were dilated. In some of the latter areas, definite and localised collections of pus were present. On the under surface of the bony roof of the orbit were numerous recently formed osteophytes.

In this case the infection had reached the diploë at several points.

2. Frontal Bone in the Temporal Region along with Temporal Muscle.- Amongst the muscle bundles the lumen of some of the smaller blood vessels was filled with septic clot, and there was diffuse polymorphonuclear infiltration round dilated blood vessels. Further, certain of the sections showed small abscesses in the connective tissue between some of the muscle bundles.

The superficial layers of the dura mater on its cerebral aspect were infiltrated by pus and the blood vessels of the attached leptomeninges were greatly dilated; in the soft membranes also, there was a fibrino-cellular exudate (acute purulent leptomeningitis).

Commentary.

It is proposed to discuss this case under the following heads: 1. The cause and duration of the infection of the air-sinuses; 2. the air-sinus responsible for the orbital abscess; 3. the osteomyelitis of the frontal bone; 4. the source of the infective thrombosis of the cavernous blood sinus; and 5. the leptomeningitis.

1. The Etiology of the Air-Sinus Infection.- It is apparent from the clinical history that infection of the nasal sinuses on the right side occurred during an acute coryza, but there is not sufficient information as to the date at which this took place. The patient was first seen by his medical attendant on account of pain about the right eye, twenty-two days before his death. The history indicates that it was about this time that the infection had passed beyond the affected air-sinuses into the right orbit. The orbital infection had occurred, as in other similar cases, by direct extension through the bony wall of an affected air cavity. A considerable amount of new reticular bone having formed in the roof of the orbit, as shown by the microscope, is a fact not inconsistent with an infection of some three weeks' duration.

2. The Air-Sinus responsible for the Orbital Abscess.- In all probability the orbital abscess arose by direct extension of the inflammation through the contiguous osseous wall of the frontal or ethmoidal air-cavities. The condition of the floor of the right frontal sinus and of the lamina papyracea of the ethmoidal cells at the time of the operation is not stated in the case records; consequently it is impossible to say from which of these two cavities the infection of the orbit arose.

It is almost certain that the sphenoidal sinus was not the primary source of the abscess since not only was there no macroscopic evidence of disease of this air cavity when examined at autopsy, but also, in cases of sphenoidal sinusitis, orbital abscess is much less frequently a complication than in cases of suppuration in the ethmoidal and frontal air-cavities.

3. Diffuse Osteomyelitis of the Frontal Bone.- A very full description of this complication of purulent inflammation of the frontal air-sinuses has been given by Dan McKenzie. The complication may arise spontaneously or as a sequel of operation upon the sinus, and is the result of the exposure of the diploic tissue to the micro-organisms.

In the present case, the diffuse osteomyelitis

was a sequel of the operation upon the sinus and, as usually happens, the infection manifested itself some days later.

In this instance, the osteomyelitis of the frontal bone, spreading from the right frontal sinus, gave rise to purulent inflammation both on its lateral and cerebral aspects. In the former situation, small deep-seated abscesses developed in the temporal muscle, with cellulitis and involvement of the cervical lymphatic nodes. On the cerebral aspect of the bone the osteomyelitis had produced a pachymeningitis and a large collection of pus in the leptomeninges distributed over the lateral surface of the right frontal and adjacent temporal lobes.

4. Infective Thrombosis of the Cavernous Blood Sinus.- In discussing the source of infection of the cavernous blood sinus in this case, certain possibilities must be considered. (a) In cases in which a subperiosteal orbital abscess forms in connection with suppuration in the ethmoidal air-cells, cavernous sinus thrombosis may develop as a further complication of the air-cell infection. In these cases it is possible that the infection may have been carried to the blood sinus along the superior ophthalmic vein. On the other hand, as some of the Haversian veins in

the orbito-ethmoidal wall open into the diploic blood spaces, infection of the red marrow may take place and thence spread to the cavernous blood sinus.

(b) The sphenoidal air-sinus may also be a primary source of the infection. There is close proximity between this air-cavity and the cavernous blood sinus and perforating veins from the former open directly into the blood spaces. For these reasons it is justifiable to assume that in cases in which the sphenoidal air-cavity is the direct source of the infection of the cavernous blood sinus, the latter occurs early in the course of the disease. In the present case the clinical history furnishes no data as to what period in the illness infection of the blood sinus took place. At the autopsy pus was found in both cavernous sinuses, but the orbital phenomena observed clinically were consistent with those met with in connection with subperiosteal orbital abscess. It is a well-known fact that thrombosis of these sinuses may occur although unsuspected during the life of the patient. If the blood spaces are only partially obliterated, or if complete obliteration is gradual, the circulation is maintained either through the sinus or the collateral vessels, so that compensation takes place.

(c) The frontal air sinus as a direct source of the infection is improbable. Cavernous sinus thrombosis seldom arises in connection with frontal sinus suppuration. In the rare cases in which it does occur, the extension is probably due to the anatomical conformation of the air-cavity. In a certain number of cases the orbital portion of the frontal sinus extends so far backwards as to come into close proximity with the spheno-parietal tributary of the cavernous blood sinus and the sinus itself. Further, in these cases some of the diploic veins of the bony wall of the orbital extension are tributaries of these blood sinuses. In the absence of clinical information as to the actual size of the frontal air-sinus in this case, we may assume that this somewhat unusual orbital extension was not present.

(d) Another possible source of the infection of the cavernous blood sinus is the spreading osteomyelitis of the frontal bone. This commenced about one week after the operation on the right frontal sinus, that is to say, some eight days before death. As the purulent infiltration had invaded the diploë in the posterior part of the orbital roof, it is quite possible that the cavernous blood sinus was infected by tributary veins from this site.

5. The Leptomeningitis.- In cases of septic thrombosis of the cavernous blood sinus which have reached the stage of disintegration of the clot with pus formation, leptomeningitis is invariably a secondary complication, though infection of the meninges may only be demonstrable in many cases by microscopic examination. In the present case, the large collection of pus in the leptomeninges over the right frontal and adjacent temporal lobes may have been secondary to the infection of the cavernous blood sinus, but on the other hand, it may have arisen secondary to the diffuse post-operative osteomyelitis of the frontal bone. In the latter instance, this would have taken place by extension of the septic thrombosis of the diploic veins through their anastomosis with the pial veins.

CASE XI. Acute Inflammation of the Ethmoidal Cells (Right): Diffuse Osteomyelitis (Frontal and Parietal Bones): Septic Thrombosis of the Cavernous Sinuses: Localised Area of Leptomeningitis: Pyaemia: Death: Autopsy.

The literature of cavernous sinus thrombosis discloses the fact that a certain number of cases of septic thrombosis cure spontaneously. This case and the next (Case XII) illustrate the process by which cure may be brought about.

D.S., aged 18, a miner, was admitted to the Ear and Throat Department, Royal Infirmary, Edinburgh, on 16th July, 1924, under the care of Dr W. T. Gardiner, F.R.C.S.E., to whom I am indebted for the following clinical notes.

Eight days before admission the patient developed an acute nasal catarrh associated with pain at the root of the nose and severe frontal headache.

Two days after the onset of the acute coryza, oedema of the right upper and lower eyelids developed, chemosis of the conjunctiva and proptosis of the eyeball supervening. It was stated that during the following three days the swelling of the eyelids diminished to some extent but again became aggravated.

Vision in the right eye was impaired.

On admission, the patient complained of pain behind the left eye and in the region of the internal canthus; he had pain also behind the right ear and on the right side of the neck. The temperature was 101·6 °F. and the pulse rate 109. The oedema, chemosis and proptosis on the right side persisted, the movements of the right eyeball being limited.

Nasal examination by Dr W. T. Gardiner, on 16th July, revealed on the right side congestion of the mucous membrane, and muco-pus beneath the right middle concha. No oedema was present. The patient's general condition did not permit of his transference to the Radiological Department.

The right ethmoidal and sphenoidal sinuses were opened by the intranasal route. A congested, oedematous mucous membrane protruded from the opened ethmoidal cells, but no pus was seen. The sphenoidal sinus was not diseased. The naso-frontal duct was patent.

A swab taken from the ethmoidal cells for bacteriological examination showed in films numerous Gram-positive cocci, diplococci and short-chained streptococci; on culture there was a scanty growth of streptococci and Staphylococcus albus.

On 17th July, Dr A. H. Sinclair reported that slight congestion and tortuosity of the veins of the fundi oculorum were present; the right pupil was immobile.

Following upon the operation on the air sinuses there was no diminution in the swelling of the orbital tissues. The temperature on the 17th July fluctuated between 99·2°F. and 100·4°F. On the 18th July, a brawny swelling appeared over the upper part of the right mastoid process; it was not tender to touch. The movements of the neck were somewhat interfered with. No signs of meningitis were present.

As the orbital condition showed no improvement, exploration with a Graefe's knife was made, but no pus was detected.

From the 19th to the 23rd July the patient's condition remained very much the same as formerly; the temperature varied from 99°F. to 100°F. No swelling of the left eyelids nor protrusion of the eyeball occurred.

On the 24th July, signs of pneumonia and pleurisy were detected on the right side, and the patient died on the 26th July, on the eleventh day after admission and on the nineteenth day of the illness.

Autopsy.- At the post-mortem the right eye was

still prominent. During removal of the calvarium, small collections of pus were found between the bone and the pericranium in the right frontal and parietal regions. The bone was not necrosed in these areas. There was also a considerable quantity of pus between the frontal bone and the dura mater (extra-dural abscess). Pus was also present in the pia-arachnoid meshes in the superior longitudinal fissure. There was no generalised leptomeningitis to be observed by the naked eye. The tissues of the right orbit contained pus.

Both pleural sacs were partially obliterated by old adhesions and the unobliterated portions contained pus. The lungs were riddled with small abscesses. The heart and liver showed toxic changes. The kidneys contained numerous pyaemic abscesses. Pus was present in the left sterno-clavicular joint.

Material removed for Microscopic Examination.- A block of bone was removed from the base of the skull. This comprised the sphenoidal and posterior ethmoidal air sinuses, and the posterior portions of the nasal cavities and orbits.

Examination of the cranial aspect of the specimen revealed on the floor of the anterior fossa on the right side a large defect in the roof of the

posterior ethmoidal labyrinth; the aperture measured 1 cm. in the antero-posterior diameter, and 0.5 cm. transversely. The bone forming the margin of the opening presented a dark discolouration due to disease. The medial side of the aperture reached the lateral margin of the cribriform plate which was intact. Its anterior margin was formed of soft bone. The inflamed mucous membrane of the underlying ethmoid cell projected slightly into the opening and showed no defect or loss of continuity. The dura mater had been separated at autopsy from the underlying ethmoidal and orbital roofs, but showed no evidence of infection having penetrated into it.

In the left ethmoidal region the bony roof of the underlying air cell was normal in appearance.

On the orbital aspect of the specimen on the right side the remains of the contents of the orbit were smeared with pus. The posterior part of the right lamina papyracea of the ethmoid bone had disappeared, the bone forming the posterior edge of the defect presenting a dark-coloured appearance. The cavity of the posterior ethmoidal cell area contained extravasated blood, the result of the intranasal operation. The mucosa on the upper part of the right side of the nasal septum was similarly

blood-stained.

The left nasal cavity and posterior ethmoidal cells were of normal appearance; the lamina papyracea was intact.

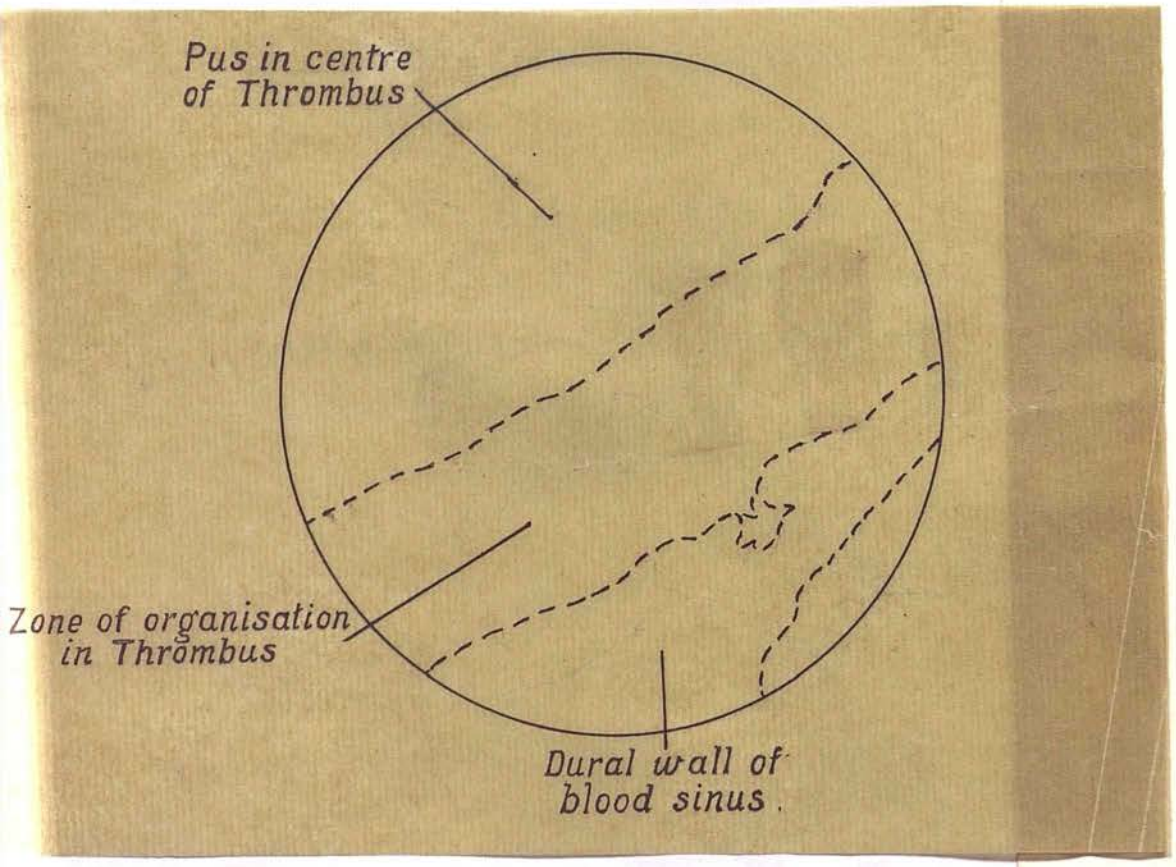
Report on the Material examined Microscopically.

The Posterior Ethmoidal Air Cells.- On the right side the mucous membrane which had not been entirely removed at the operation was oedematous and polypoid and showed large and small round mononucleated cells together with plasma cells. The walls of the blood vessels were not thickened and the epithelial lining was intact.

A right posterior ethmoidal air cell present in the sections was full of blood clot; the latter showed foci of infection, colonies of bacteria being present in these areas.

The parts of the bony walls of the air cells that remained showed a certain amount of osteoclasis; considerable osteoblastic activity was also present. In many places "reticular" bone was being formed in the deeper mucosal layers lying upon the surface of the preformed bone.

In one of the left posterior ethmoidal cells the mucous membrane was oedematous in certain areas. The



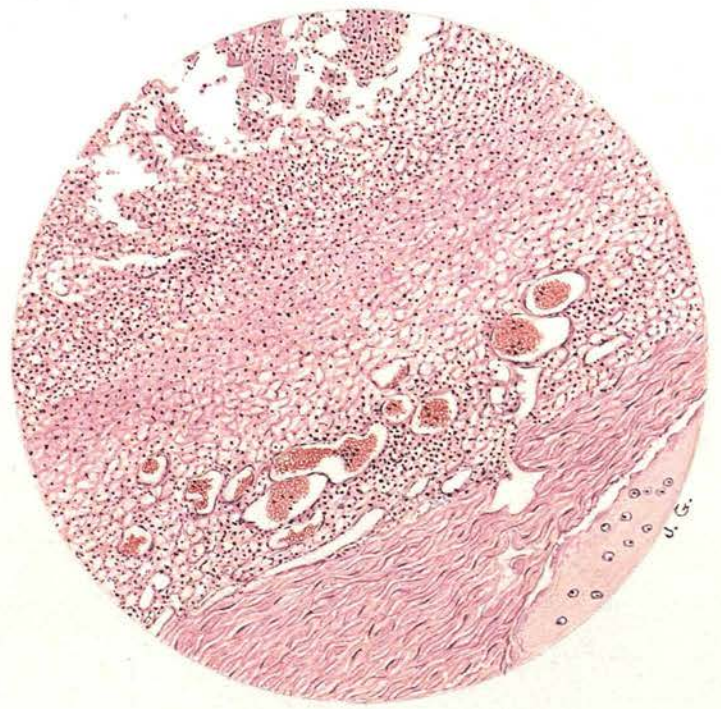


Fig.43.- Commencing organisation of the septic thrombus in one of the blood spaces of the cavernous sinus. In the centre of the blood space the clot has disintegrated into pus; the mural portion of the thrombus is being invaded by young blood vessels and fibroblasts.
(Stained by haematin and eosin.)

To face page 160.

mucosal veins were dilated and a few of them were partly filled by septic clot (retrograde thrombosis). No changes of a chronic inflammatory nature were found in any of the left posterior ethmoidal cells.

The Sphenoidal Air Sinuses.- Only one air cavity was present in the body of the sphenoid bone. Its position indicated that it was the right cavity. There were no inflammatory changes in the mucous membrane other than those usually regarded as of terminal origin.

The Orbits.- The walls of the ophthalmic veins on both sides had disappeared and pus was present in the surrounding orbital tissues.

The Cavernous Blood Sinuses.- The blood spaces of both cavernous sinuses were full of septic clot, the centre of which, in most instances, had broken down with the formation of pus. On both sides and in many places organization of the clot was commencing; small recently formed blood vessels and young fibrous tissue cells were invading the portions of the thrombus lying in relation to the wall of the blood space.

The Leptomeninges.- Acute leptomeningitis existed in the pia-arachnoid membranes present in the sections, namely, around the Gasserian ganglia and

the posterior clinoid processes.

Commentary.

In this case, the disease began acutely and at first pursued a rapid course; infection reached the right cavernous blood sinus which quickly became thrombosed. After a few days, however, the infection was restrained and thereafter the further progress was slow.

The actual details of the spread of the infection and the precise relationship of some of the phenomena to it cannot be defined with absolute certainty. The following, however, in the writer's opinion, is the most probable course of events.

Nineteen days before death, the patient developed an acute coryza. From the clinical history supported by the pathological changes found at autopsy and on microscopical examination, the right ethmoidal air cells became infected at this time. The infection spread to the bony walls of these cells, giving rise to cario-necrosis of the right lamina papyracea (medial wall of orbit) and of the roof of the posterior ethmoidal cells. The oedema of the eyelids on the right side, which occurred two days after the onset of the acute nasal catarrh, was due to the infection of the orbito-ethmoidal wall.

A lack of pathological material prevents the demonstration of the manner in which the diffuse osteomyelitis arose in the right fronto-parietal region; the writer is not prepared to exclude a direct extension of the infection from the lamina papyracea and roof of the posterior ethmoidal cells, although it is not very probable from a consideration of the anatomical relationship of these parts.

Early in the course of the infection of the lamina papyracea and roof of the posterior ethmoidal cells, the right cavernous sinus became infected, the infection reaching it by tributary veins from the diploë either directly or by way of the ophthalmic venous system. The aggravation of the orbital changes which occurred five to six days after the onset of the acute coryza and which was associated with impairment of vision, was due to the infection of the right cavernous sinus.

The pericranial abscesses in the right frontal and parietal regions and the extra-dural abscess in relation to the right frontal bone were secondary to the neighbouring osteomyelitis. Again, since the pia-arachnoid membrane in the right superior longitudinal fissure contained a large amount of pus as compared with the other parts of the leptomeninges and

since this was in direct anatomical relationship to the extra-dural abscess and to the infected bone, it is probable that this localised collection of pus arose as a further complication of the osteomyelitis.

On the other hand, the basal meningitis, demonstrated only by the microscope, was probably secondare to the septic thrombosis of the cavernous sinus.

Had infection reached the leptomeninges through the large defect in the bony roof of the posterior ethmoidal labyrinth, it is probable, firstly, that the overlying dura mater would have shown some signs of the infection having passed through it, and, secondly, that a localised collection of pus would have been present in relation to the defect.

After the right cavernous sinus had become infected, the septic thrombotic process spread through the veins of the circular sinus to the left cavernous sinus which in turn became the site of a septic thrombus. The formation of the clot on the left side was slow since the classical orbital signs were never present on this side. Extension of the clot along tributary veins gave rise not only to the basal meningitis already referred to, but also to septic thrombosis of the ophthalmic veins and doubtless of diploic, ethmoidal, and mucosal veins. The swelling

over the right mastoid process, which occurred ten days after the onset of the acute nasal catarrh, was due probably to extension along the superior petrosal sinus into the transverse sinus and thence along the mastoid emissary vein. Lastly, the manifestations of general pyaemia were sequelae of the thrombosis of the cavernous sinus.

CASE XII. Acute Infection of the Left Sphenoidal Air Sinus: Cavernous Sinus Thrombosis with Organisation of the Clot: Leptomeningitis: Operation: Death: Autopsy.

At a meeting of the Scottish Society of Otology and Laryngology held on 12th June, 1922, Dr J. S. Fraser, F.R.C.S.E., read the notes of a case, J.O.B., male, aged 45, who had died from acute leptomeningitis secondary to cavernous sinus thrombosis. Dr Fraser illustrated his remarks by exhibiting the brain and microscopical sections of the left sphenoidal air cavity and left cavernous blood sinus.

I am indebted to him for the opportunity kindly given to me of examining the microscopical preparations made by him, for the clinical notes, and for permission to include the case in my series on the investigation of the paths of infection.

After thrombosis of the cavernous sinus had occurred, the patient in the present instance did not live more than one or two days longer than in the previous case (Case XI.); organisation of the clot, however, had advanced to a further stage. In contrast to the early granulation tissue present in the thrombus in Case XI, in the case now to be considered

a comparatively large amount of well-formed fibrous tissue had been developed and the circulation through the left cavernous sinus - the one chiefly affected - had been partially re-established.

J.O.B., a male, aged 45, was admitted to a nursing home on the 20th December, 1919. Four days previously (16th December) he complained of severe nasal catarrh associated with sore throat. For two days the discharge from the nose was profuse. It then ceased somewhat suddenly, and a painful swelling appeared at the upper and medial angle of the left orbit. The swelling increased rapidly in size and considerable pain was experienced. The temperature rose to 101°F.

On admission it was found that the changes in the left orbit were those characteristic of cavernous sinus thrombosis - proptosis and restricted movements of the eyeball with chemosis of the conjunctiva; the eye was completely closed owing to swelling of both eyelids. No tenderness was elicited over the left frontal sinus. Anterior rhinoscopy revealed a marked deviation of the septum to the left; no pus was seen in either nasal cavity. Posterior rhinoscopic examination was not successful. The tongue was very dry. No facilities were at hand for X-ray examination, and,

as the condition was urgent, immediate operation was carried out.

First operation.- At 1 p.m. on the 20th December, under local anaesthesia, the anterior end of the left middle turbinal was removed and the anterior ethmoidal cells opened; no pus was evacuated. On the same evening the external swelling had extended on to the left cheek. The temperature was 102°F., and the pulse 112. During the night the patient was slightly delirious.

On 21st December, he was seen in consultation with Drs. Logan Turner and J.V. Paterson. There was now pronounced chemosis of the conjunctiva and the movements of the eyeball were very restricted. Dr Paterson reported that the left optic nerve was still functioning and that the visual field, roughly tested, was fairly normal. The patient could decipher the position of the hands of a watch at a distance of six inches. It was decided that the higher air sinuses on the left side should be opened.

Second operation.- On the evening of 21st December, under a general anaesthetic, Dr Fraser explored through an external incision the left frontal, ethmoidal and sphenoidal air sinuses, but no pus was found. On incising the periosteum on the medial wall of the orbit, no abscess was detected in that

situation. Although bleeding interfered somewhat with accurate observation, it was possible to see that the lining membrane of the sphenoidal air sinus was congested. The wound was lightly packed and no stitches were inserted.

During the three days following this operation, the temperature varied, rising as high as 103°F.; the pulse and respirations were accelerated. On the fourth day the temperature fell to normal, and the pulse rate was 94, but the respirations remained between 36 and 42, The patient was still somewhat delirious and attempted to get out of bed. The mouth and throat continued to be very dry.

On 26th December, great improvement was observed in the movements of the left eye, and the swelling of the eyelids had to a very appreciable extent disappeared. (In the light of the pathological changes found subsequently on microscopic examination of the cavernous blood sinuses, this observation is important.) On this date, Dr Paterson reported that there was some congestion of the veins of the disc, but no optic neuritis.

On 27th December, on account of the patient's mental excitation, he was examined by Dr Edwin Bramwell, who found no evidence of organic change in

the nervous system; there was congestion at the base of the right lung and this probably explained the rapid respiration. The temperature remained normal for two days.

On 29th December, recrudescence of the delirium was followed by slow cerebration and the onset of coma. As these phenomena suggested an extension of the infective process into the anterior cranial fossa, a further operation was decided upon.

Third Operation.- On the evening of the 29th December, the left frontal sinus was laid freely open and its posterior wall removed along with the osseous roof of the orbit. No extra-dural abscess was found. The dura mater pulsated and did not bulge; on incising it, no sub-dural abscess was present. On exploration of the frontal lobe, no abscess was found.

The patient passed a restless night and on the following day became almost completely comatose. Kernig's sign was present; the coma deepened, the temperature rose to 103°F., and death occurred on the evening of 1st January, 1920.

The whole duration of the illness was therefore seventeen days after the onset of the acute nasal catarrh.

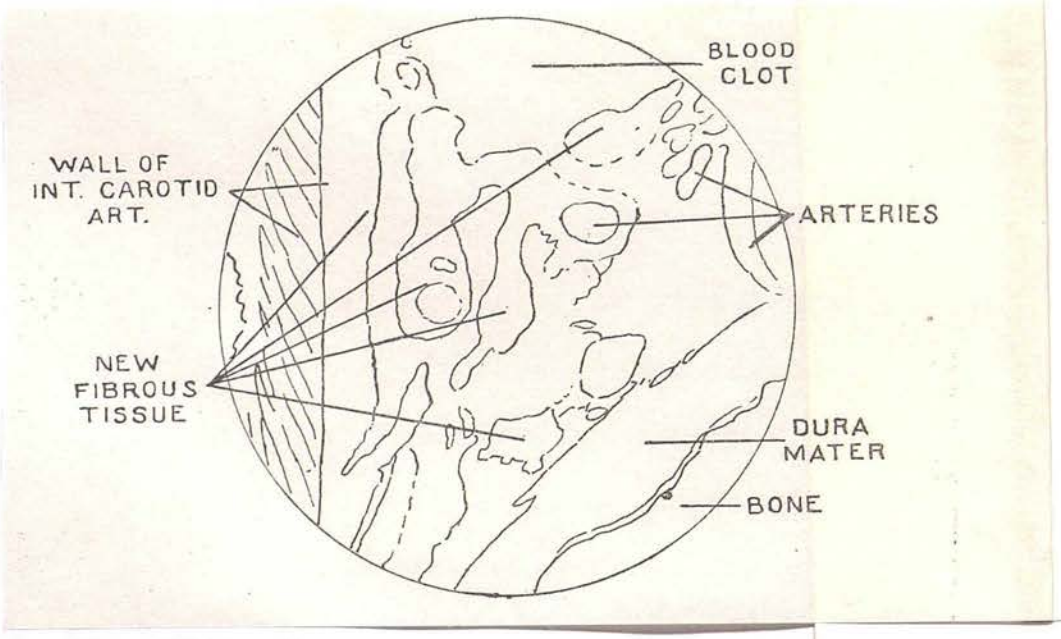
Autopsy.- A considerable quantity of thick,

sticky pus was present in the subarachnoid space over both frontal lobes, and very slight meningitis over the lower surface of the brain. The vessels on the cerebral surface were greatly congested. No intra-cerebral abscess was found. The left maxillary antrum was completely filled by an almost solid mass of gelatinous yellow pus.

Bacteriology.- From a portion of the mucous membrane removed from the left frontal sinus at the third operation, staphylococci and diphtheroids were obtained on culture.

At the post-mortem, cultures were made by Dr W. R. Logan. From the pus on the frontal lobes, no bacterial growth was obtained; from the pus in the maxillary sinus, a staphylococcus, a lanceolated Gram-positive diplococcus (probably Pneumococcus) and a short diphtheroid bacillus were isolated.

Preparation of the Material for Microscopic Examination.- A block comprising the sphenoidal air cavities and cavernous blood sinuses was removed from the base of the skull. After decalcification, this was embedded in celloidin; serial sections in the horizontal plane were made from above downwards. The series comprised 750 sections, every fifth section being stained and mounted.



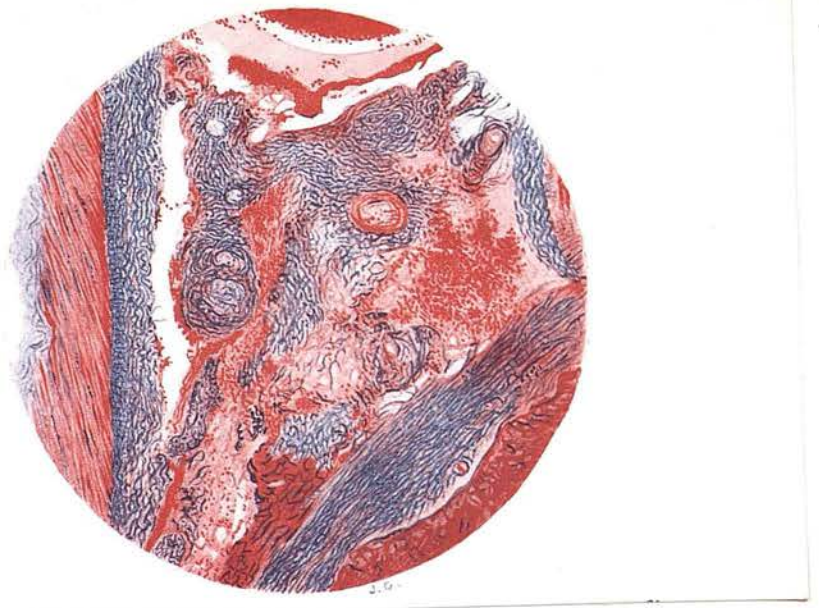
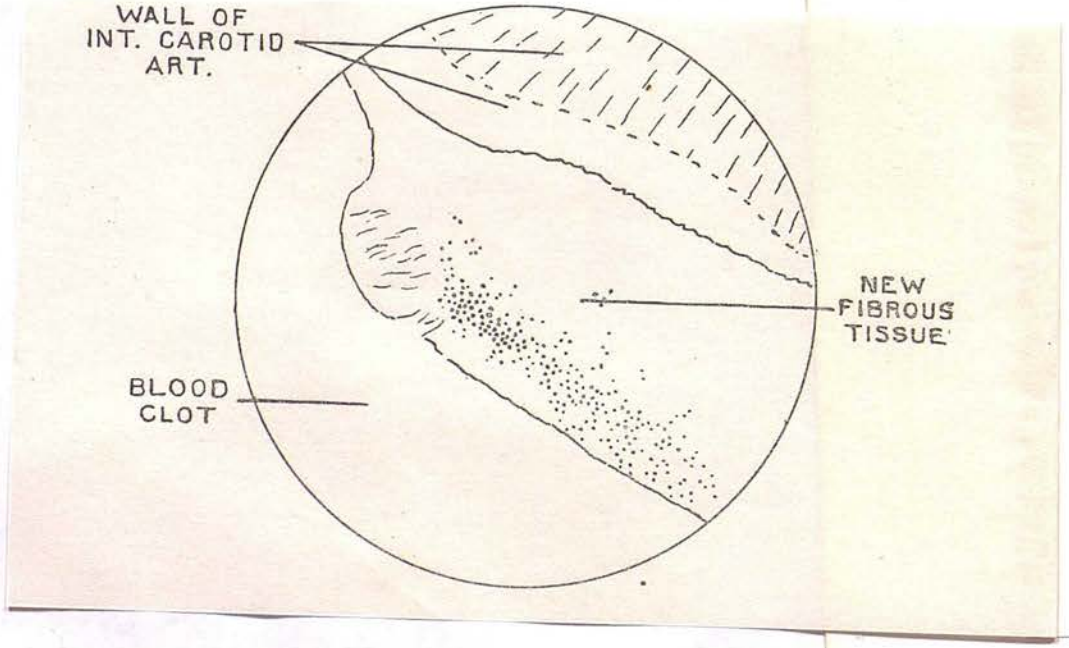


Fig.44.- Horizontal section through the left cavernous sinus showing new fibrous tissue in the blood spaces; the small arteries are in the original trabeculae of the sinus. (Stained by Heidenhain's Azan method.)



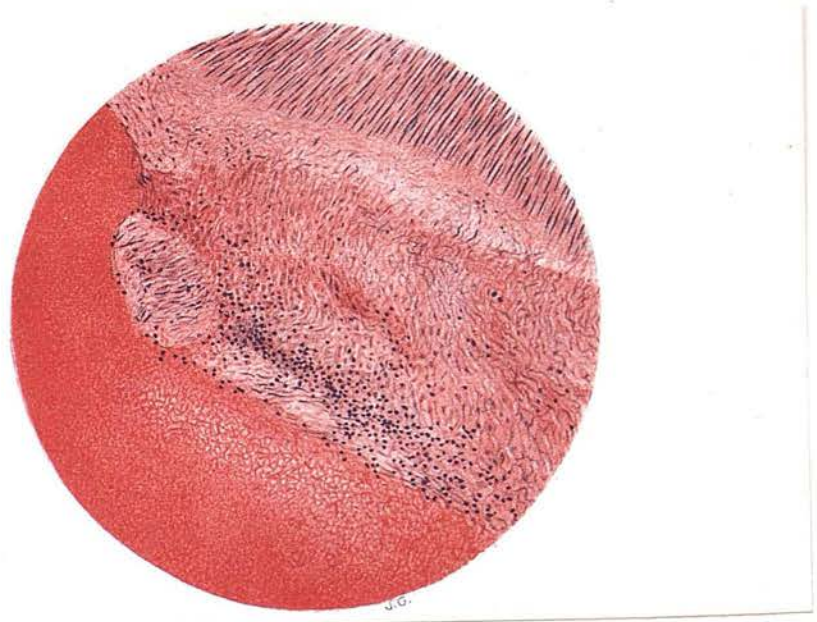


Fig.45.- Section similar to the above; in the new fibrous tissue there is a collection of polymorphonuclear leucocytes indicating an infective focus. (Stained by haematoxylin and eosin.)

To face page 171.

Report on the Material examined Microscopically.

1. Cavernous Blood Sinuses.- Many of the blood spaces of the left cavernous sinus were almost completely obliterated by fibrous tissue (Figs.44,45). In others, masses of fibrous tissue were attached to the walls of the blood spaces and projected into their interior. The remaining blood spaces were filled with post-mortem clot. The fibrous tissue was of recent formation, being very cellular; the cells were large, elongated, and with darkly staining nuclei. Within the masses of new fibrous tissue, small collections of pus were present, and around some of these infectious foci there was diffuse infiltration by polymorphonuclear leucocytes. Here and there, blood-clot was adherent to the walls of the blood sinuses. These clots showed collections of polymorphonuclear leucocytes both near the free surface and scattered sparsely throughout the thrombi. The clots were almost structureless, but the outlines of red blood corpuscles could still be seen in some areas; fibrosis had not occurred.

On the right side, the blood spaces of the cavernous sinus for the most part persisted and were filled by post-mortem clot. There were, however, a few small masses of new fibrous tissue with

polymorphonuclear cell infiltration, as on the left side. One of the spaces was partly filled by recent blood-clot, in the surface layers of which were two dense collections of polymorphonuclear leucocytes; this clot extended into the posterior circular sinus.

2. The Meninges.- Several thrombosed veins were found in certain situations in the dura mater covering the floor of the middle cranial fossa, e.g. the lateral wall of the left cavernous sinus, the upper surface of the dorsum sellae, etc. No thrombosed pial veins were seen. But in this connection it must be borne in mind that soon after septic thrombosis of a pial vein takes place, the thin wall breaks down and the site of the vein can no longer be recognised in the pus (Case I,, pg.49).

The pial meshes in relation to the Gasserian ganglion, to the 5th nerve trunks and to the upper surface of the pituitary gland were infiltrated by pus.

3. The Bone Marrow.- The left sphenoidal air sinus was of larger dimensions than the right and extended upwards to a higher plane. Hence the upper part of its right wall came into relationship with the right cavernous blood sinus. In this situation, one red marrow space with a contiguous Haversian

system was found infected. No similar infection was present elsewhere in the bony walls of either sphenoidal sinus.

4. The Mucous Membrane of the Sphenoidal Air Sinuses.- In both air sinuses the mucous membrane was oedematous; the smaller blood vessels were dilated and active diapedesis was occurring through the walls of some of them. The layers of the mucosa were infiltrated by large and small mononucleated cells and by scattered polymorphonuclear leucocytes. At places there were small dense collections of cells. The infiltration was most marked under the epithelial lining. Haemorrhages were present, probably of traumatic origin. For the most part the lining columnar epithelial cells were intact and were very actively secreting. The mucous membrane tended to be polypoid. The cavity of the right air sinus contained mucus, while that on the left side contained blood-clot and polymorphonuclear leucocytes.

A few of the Haversian systems contiguous to the periosteal layer of the mucous membrane showed osteoclastic activity.

Origin and Progress of the Infection.

As pus was present both in the maxillary and sphenoidal air sinuses, the question arises as to

which of these cavities provided the primary focus of infection of the cavernous blood sinus.

Most authorities are agreed that in those cases in which the maxillary sinus has been regarded as the origin of the cavernous sinus affection, an associated septic focus in one of the higher air cavities is more probably the source of the infection. Although the material available in this case does not solve the problem, it is probable that the sphenoidal sinus was the focus of the infection.

As argued in previous cases, infection of the cavernous blood sinus occurred by way of the blood stream.

In the present case, after thrombosis of the left cavernous sinus had occurred, the patient lived sufficiently long to allow of organisation of the clot by fibrosis. Little extension had taken place into the right sinus. These two facts indicate that the infecting micro-organisms cannot have been very virulent in relation to the protective powers of the tissues. Such bacteriological examination as was made bears out this thesis; the only micro-organisms found in the case were a staphylococcus, a diphtheroid bacillus and a pneumococcus, the last named being present in the maxillary sinus.

Generally speaking, staphylococci and diphtheroid bacilli are less virulent than the strains of streptococci usually met with in suppuration. Even if the pneumococcus were one of the micro-organisms responsible for the thrombosis, it must be remembered that while it is usually a virulent infecting agent, certain strains of a less virulent type exist.

A thrombus having formed in the left cavernous sinus became organised, and circulation was re-established through the diminished lumen of the blood sinus and its collaterals (anterior circular sinus, pterygoid plexus, etc.). The gradual disappearance of the orbital oedema causing the exophthalmos is thus explained.

If the clot was aseptic at first, it became infected later; but it is probable that infection was present from the onset, the micro-organisms remaining localised, their site being recognised in the sections as small collections of polymorphonuclear leucocytes (Fig. 45).

Some nine to ten days after the onset of the thrombosis in the blood sinus, acute leptomeningitis occurred. This complication was due to the infection spreading along tributary veins. As

demonstrated in previous cases of the series, septic thrombosis of a pial vein results in its thin wall breaking down, the pus escaping into the pial meshes. It is more probable that, in this case, extension along the pial veins was a slow process. If rapid, it would have been due to relative exacerbation of the virulence of the micro-organisms; as a result, not only would the remaining blood spaces in the left sinus have been filled with newly formed septic clot, but extension would have taken place to the right sinus, with consequent more or less occlusion by recently formed septic thrombus.

So long as the infection was confined to the blood spaces of the cavernous sinus, it was restrained; consequently it was limited almost entirely to the left cavernous sinus, and part of the thrombus underwent organisation by fibrous tissue. The re-establishment of the circulation through the sinus, assisted by the compensation obtained from the collateral circulation, explained the gradual disappearance of the orbital oedema and exophthalmos.

Having reached the pia-arachnoid space, the infection was no longer restrained, but widespread infection of this new ground occurred. The development of acute leptomeningitis - so frequently a

secondary complication of cavernous sinus infection - caused the fatal termination. Cure of the meningitis could only have taken place in the event of the infection being not only restrained but controlled in the pia-arachnoid.

Summary.- A primary acute inflammation of the left sphenoidal air sinus resulted in the formation of a mildly infected thrombus in the left cavernous blood sinus. The clot became organised and circulation was re-established through the diminished lumen of the blood sinus and its collaterals and thus the orbital oedema gradually disappeared. The micro-organisms in the thrombus remained localised, but the infection eventually reached the pia-arachnoid membrane and the patient died of acute leptomeningitis.

CASE XIII. Acute Suppurative Otitis Media: Operation: Cavernous Sinus Thrombosis: Recovery.

In an analysis of 123 consecutive cases in which operations were performed for the relief of the mastoid, labyrinthine and intracranial complications of suppurative otitis media published by J. S. Fraser and J. K. Milne Dickie in 1912, reference was made to a case of cavernous sinus thrombosis which had recovered. In this patient, the primary seat of the infection was in the left ear, but the secondary thrombus in the cavernous blood sinus was manifested on the right side.

Dr Fraser has kindly given me access to his notes on the case and allowed me to include it in the present series, which is thus made complete from the pathological standpoint. The following is a résumé of the course of the illness and subsequent history of the patient.

J. B., male, aged 61, was admitted, on 11th April 1911, into the Ear and Throat Department of the Royal Infirmary, Edinburgh. He suffered from acute suppuration of the left middle ear, the discharge being of nine weeks' duration. A week before

admission the discharge diminished and severe pain developed in the ear.

On examination, pus was seen in the external acoustic meatus; there was considerable tenderness on pressure on the mastoid bone, and slight oedema superficial to the tip of the process and on the tendon of the sterno-mastoid muscle. Hearing was only slightly impaired. The upper air passages were normal. The temperature registered 99·8°F. The patient was admitted.

The Schwartze operation was performed; pus was present in the antrum, and the lining membrane of the cells of a well-developed pneumatic mastoid process was swollen. The lower part of the wound was left open. On the two following evenings the temperature was 100·4° and 101°F. respectively. On the sixth day after operation, the temperature was still slightly elevated; the wound was granulating, but tenderness and swelling below the mastoid process was more pronounced. Consequently, on 19th April, its tip and inner plate were removed and a quantity of pus was evacuated medial to the sterno-mastoid muscle. The wall of the sigmoid portion of the transverse sinus was of normal appearance. As the deeper osseous meatus was narrowed, a modified

Case XIII.

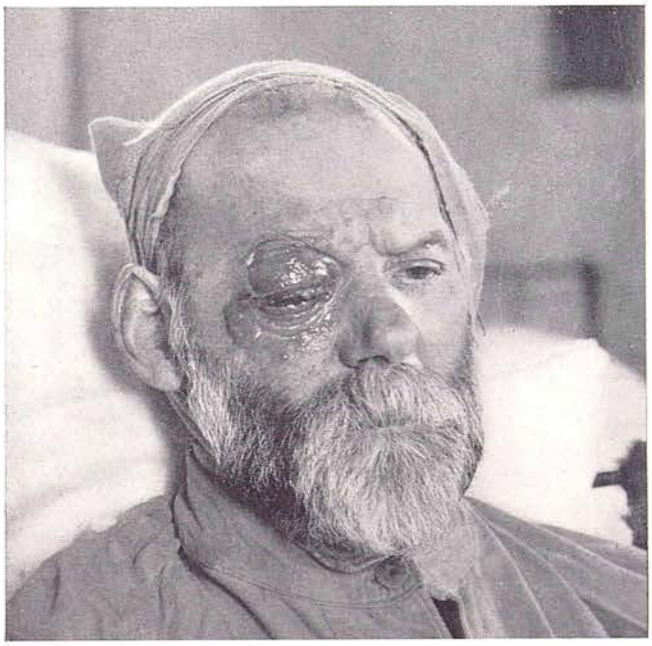


Fig.46.- The illustration is from a photograph of the patient on 25th April and shows the orbital phenomena typical of thrombosis of the right cavernous blood sinus.

To face page 180.

radical operation was carried out, the "bridge" being removed. At this stage the lateral canal was accidentally opened. The abscess cavity in the upper part of the neck was at first packed with gauze but later a drainage tube was inserted.

The temperature now ran a normal course.

On 20th April, the right eye became slightly painful and the conjunctiva injected. On the 22nd, marked chemosis of the conjunctiva was present, but no exophthalmos or oedema of the eyelids developed at this date. Vision in the right eye was almost completely lost, the patient being only able to distinguish between light and darkness. On 23rd April, an examination of the eye was made by Dr W. G. Sym, who diagnosed the condition as septic thrombosis of the ophthalmic vein. On 25th April, the right eyelids were oedematous and the eyeball proptosed and fixed (Fig. 46).

During the whole of this period the temperature ranged between 97° and 98°F. and the pulse was normal. The patient's general condition was good. The left eye remained unaffected. Pus still continued to discharge from the wound in the neck.

On 7th May, the swelling of the right eye had commenced to subside, but a considerable quantity of

purulent discharge was secreted in the conjunctival sac. Anterior and posterior rhinoscopy revealed no evidence of pus in the nasal cavities.

A counter-opening in the neck was necessary before final healing of the abscess took place. The patient was discharged on 8th July.

On 16th August 1911, he reported at the Department. Functional examination of the left ear revealed complete loss of hearing and of the vestibular reactions. Dr Sym, who again saw the patient, considered it advisable to enucleate the right eyeball on account of the ulcerated condition of the cornea. In November 1913, the patient again reported at hospital. The left ear was dry and epithelialisation of the mastoid cavity was complete.

Bacteriology.- At the first operation on the 12th April, the swab from the mastoid cells disclosed on culture in broth long chains of Gram-positive cocci; subcultures revealed micro-organisms resembling Streptococcus pyogenes.

Commentary.

Of recorded cases, the larger number of recoveries from cavernous sinus thrombosis occur when the primary focus of infection is in the ear, in

some of them recovery being assisted by operation on the transverse sinus.

In the present case, infection spread from the middle ear by one of the anatomical venous routes into the cavernous blood sinus.

Since the patient recovered, no direct examination of the intracranial structures involved in the course of the disease was possible. Hence the reason of the cavernous sinus thrombosis being manifested by the classical signs on the right side whereas the primary inflammatory focus was in the left middle ear can be a matter only of pure conjecture. Any discussion as to the possible explanation would be so extremely hypothetical that, in the writer's opinion, it would be of little or no value.

For recovery to have taken place the thrombus in the cavernous sinus must have been either aseptic or one mildly infected. The infection, restrained at first, was later controlled; organisation occurred in the manner indicated by the two previous Cases XI. and XII.

NOTE ON

INFECTION OF THE CAVERNOUS BLOOD SINUS BY WAY OF THE CAROTID VENOUS PLEXUS

NOTE ON
INFECTION OF THE CAVERNOUS BLOOD SINUS
BY WAY OF THE CAROTID VENOUS PLEXUS.

In the majority of cases in which the cavernous sinus is the site of septic thrombosis, the infection reaches it from a primary focus in front, namely, from the face, nasal cavities, and ethmoidal labyrinth or from below and medially, namely, from the sphenoidal air sinuses. In a certain number of instances, however, the cavernous sinus is infected from behind, namely, from the middle ear cleft.

While carrying out the investigation which forms the subject of this Thesis, the writer was fortunate in obtaining material from cases of the last group (Cases IV, V, VIII) and in having placed at his disposal the clinical notes of one case which recovered (Case XIII).

As already stated (pg.87) in most of the recorded cases of septic thrombosis of the cavernous sinus of otitic origin, the infection has spread forward by progressive thrombosis of the transverse and petrosal blood sinuses. This method of infection was well exemplified in Case VIII.

Of late years, considerable and increasing

attention has been directed to infection reaching the cavernous sinus from the middle ear by way of the carotid venous plexus. On anatomical grounds, as already mentioned (pg. 26) such a route of infection is possible and a certain number of cases have been published in which the author has claimed that the infection travelled by this venous pathway.

It would be outwith the purpose of this Thesis to analyse these cases individually; it is sufficient to indicate again that in none of them have the data given been sufficient to exclude other pathways whereby the infection might have reached the cavernous sinus. The present investigation has amply proved that it is not enough to make a microscopical examination of the carotid venous plexus and if thrombosis is found within the veins composing it, to conclude straightway that this was the initial route of infection.

Although it was not the primary object of the writer's investigation to ascertain the correctness or otherwise of the views held in regard to the carotid venous plexus as a pathway of infection, it is of interest to collect the information on this point available from the cases of this Series.

1. <u>Cases in which the Cavernous Sinus was</u>

infected from the Middle Ear Cleft (Cases IV, V, VIII).

In Case IV, veins in both carotid venous plexuses were thrombosed, but it was argued (pg. 87) that this route could be definitely excluded as the primary pathway of infection. In this case, by an unfortunate oversight, the transverse and petrosal sinuses were not examined and hence it can only be a matter of conjecture as to what pathway the infection took.

In Cases V and VIII, it was demonstrated at autopsy that thrombosis of the inferior petrosal sinus had occurred and therefore material was not examined microscopically. Even if the carotid venous plexus had been thrombosed in either or both of these cases, to maintain that infection had reached the cavernous sinus by this route and that the infection of the inferior petrosal sinus was a secondary manifestation would be to advance a most improbable interpretation rather than one which is almost a certainty.

Cases in which the Cavernous Sinus was infected from a focus other than the Middle Ear Cleft (Cases I, II, III, VI, VII, XI).

On the other hand it might reasonably be asked if any of the cases of the present Series in which the primary focus of infection was not situated in the ear, showed infection of the carotid venous plexus.

The condition in Case I is instructive and well

exemplifies how an erroneous deduction might be drawn from an examination of sections from only one portion of the carotid venous plexus. Sections at a particular level in the carotid canal showed a septic thrombosis of one of the veins of the carotid plexus. On following up the infected clot, however, it was found to be continuous with pus in the adjacent diploë; further, sections showing the plexus accompanying the carotid artery passing forward through the cavernous sinus, demonstrated that the veins here were not thrombosed (see Fig.7, which is a microphotograph taken from one of these sections). Obviously the infection seen in the carotid venous plexus in this instance was secondary to the osteomyelitis which again was secondary to the septic thrombosis of the cavernous blood sinus.

Similarly in Case II, a few of the veins of the carotid venus plexus in the carotid canal on the right side showed early thrombosis, whereas the plexus accompanying the artery in its course through the cavernous blood sinus was not thrombosed. In this case also, there was extensive infection of the diploë.

In Case III, the material available showed only the portion of the carotid venous plexus accompanying

the carotid artery in its course through the cavernous sinus; in this part the veins of the plexus were not thrombosed.

Parenthetically a point of pathological interest may be touched upon. In Cases I, II and III the septic thrombosis of the cavernous sinus was fulminating in type and in each instance the septic process had extended widely along tributary veins. It might be a matter of surprise and at first appear to have some significance to the question now under discussion that the veins of the carotid venous plexus nearest to the infected cavernous sinus were not the site of secondary septic thrombosis. As a matter of fact, in these three cases, the veins of the carotid venous plexus were not the only tributaries of the cavernous sinus into which the thrombus had not extended. For example, in Case I, some of the intercavernous veins - of larger calibre, moreover, than those forming the carotid plexus - were not the site of secondary septic thrombosis. Why some of the tributaries should be affected and not others is a general pathological question and it is not proposed to enter here upon a discussion regarding the determining factors.

In association with these last cases, the writer

would refer again very briefly to Case IV. The partial infection of the carotid venous plexus in Cases I and II strengthens the argument advanced in the Commentary of Case IV that the infection present in the plexus had a similar origin, namely, the adjacent diploë.

Case VI is highly instructive from the point of view of the subject now being considered. The septic thrombosis of the cavernous sinus in this case was fulminating in type and secondary to a focus situated in the ethmoidal labyrinth. The carotid canal on the right side - the same side as the cavernous sinus first thrombosed - was full of pus and the veins of the left carotid venous plexus were filled completely by septic clot. Cases of septic thrombosis of the cavernous sinus which are fulminating in type arise from a primary focus in the middle ear cleft - for example Case IV of this Series - and there is no reason to suppose that a similar condition of the carotid venous plexus to that present in Case VI might not occur in such a case. In these circumstances, unless a careful and wide microscopical examination were made and the deductions therefrom critically examined, the erroneous conclusion which might be drawn is obvious.

In Case VII the primary focus was in the sphenoidal air sinuses. Thrombosis of the cavernous sinus was not far advanced and was not suspected until microscopical evidence revealed its presence. In this case the thrombotic process in the anterior part of the cavernous sinus was just proceeding into the veins of the carotid venous plexus. Hence the case shows that in certain instances the clot from the cavernous sinus extends directly into the openings of the veins of the plexus.

Case XI is as equally important to the subject as Case VI. In contrast to the latter, the septic thrombosis in Case XI was restrained in type, the patient living some thirteen days after the cavernous sinus had become infected from a primary focus in the ethmoidal labyrinth. In this case both carotid canals were full of pus.

The above facts are sufficient to show that in any particular case very complete evidence is required before it is accepted as proved that the carotid venous plexus is the pathway of infection from the middle ear to the cavernous sinus.

V. INFECTION OF THE INTRACRANIAL STRUCTURES BY DIRECT EXTENSION THROUGH THE BONE.

V. INFECTION OF THE INTRACRANIAL STRUCTURES BY DIRECT EXTENSION THROUGH THE BONE.

Macroscopically, infection of the intracranial structures by direct extension through the bone is a frequent path of infection.

H. Kuhnt, who studied the subject in connection with the frontal sinus as far back as 1895, bases his observations upon the published records of 17 cases of sinus suppuration with intracranial complications. Of these, macroscopically, 14 showed disease of the cerebral bony wall with or without actual perforation; in 2 the infection had spread by veins as a thrombo-phlebitis, no disease of the bone being visible; in one case the information was unreliable; G. Killian, writing in 1900 on the same subject, cited 30 observations, which included those reported by Grünwald, Kuhnt, and Dreyfuss. Disease in the osseous cerebral wall of the frontal air cavity was recognised macroscopically in 25 cases with intracranial infection; this was secondary to chronic sinus suppuration. H. Luc has asserted that it is exceptional to find the bony wall intact in cases in which an intracranial complication has developed. P. H. Gerber's figures, also dealing with the frontal sinus and published in

1909, were based upon a still larger number of observations collected from various sources and including some of those above referred to. They corroborate the statement of the previous writers. In 87 cases, in which data were furnished, direct contact infection through the posterior wall of the sinus was found in 52, giving 59·7 per cent.

Of twenty cases examined by Logan Turner, direct extension through the bony wall was present in seventeen. In this series, therefore, although too small to permit of any generalisation, direct extension occurred in 85 per cent., a percentage greatly in excess of that noted by Gerber's statistics.

If further proof of the frequency of the pathway of infection by direct extension through the bone were necessary, it is furnished by a summary of cases of orbital infection due to air sinus suppuration. In thirty-nine cases of inflammatory orbital complication treated by Logan Turner by external operation, disease of the sinus wall adjacent to the orbit was found macroscopically in twenty-five (64 per cent.) of the cases.

Direct extension through the bone has usually been regarded as a complication of the chronic type of sinus disease, it being argued that although the

history of the case may suggest the recent origin of the inflammation, the apparently acute onset is in reality an exacerbation of a long-standing suppuration. Differentiation, however, between the acute and chronic character of the suppuration in the air sinus is not always easy. Even when the air sinus is opened, it is often impossible to determine from the macroscopic appearance of the lining mucous membrane whether the inflammation is of recent origin or has existed over a considerable period of time. The microscope may give the necessary information.

Unfortunately, the term "chronic" is employed in relation to very varying periods of time. K. Wittmaack has demonstrated by microscopic investigation of the air-cells removed at operation in cases of acute mastoiditis that changes in the bone, hitherto generally regarded as indicating long-standing inflammation, commonly occur within so brief a period as three weeks from the onset of the infective process. J.P. Stewart, working on the same subject in the Ear and Throat Department of the Royal Infirmary, Edinburgh, has corroborated these observations. The consideration of the cases of accessory sinus disease in the Series has caused the writer to modify his views as to the time required for the production of osteoclastic and

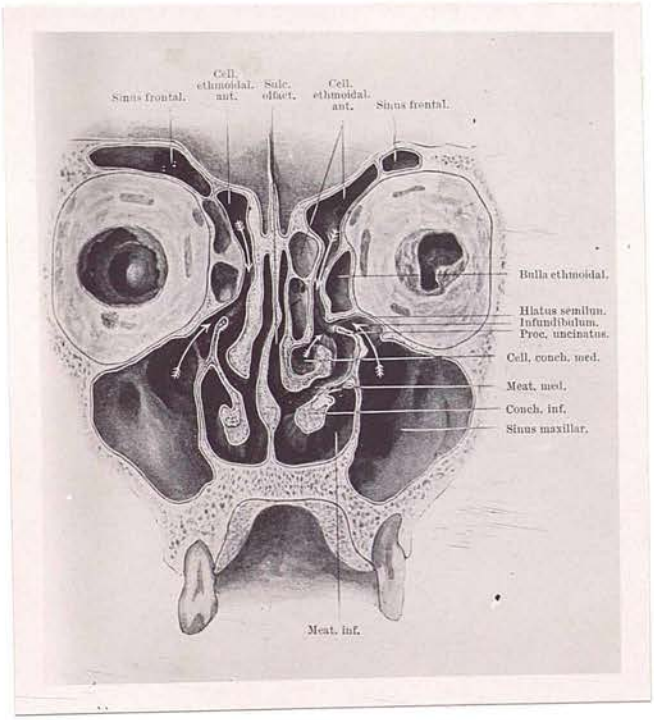


Fig.47.- Reproduced by kind permission of Dr A. Logan Turner from <u>The Accessory Sinuses of the Nose</u>. The illustration represents a coronal section, viewed from behind, and made on the plane of the maxillary antral orifices. The close relation of the frontal, anterior ethmoidal, and maxillary sinuses to the orbit is seen. In the specimen illustrated, the olfactory groove is deep and narrow.

To face page 195.

osteoblastic changes. He had previously regarded them as indicating a pathological process of much longer standing.

The Anatomy of the Nasal Cavity and of the Nasal Accessory Air Sinuses in relation to the Cranial Cavity.

In the cases of the present Series in which infection of the intracranial structures had occurred by direct extension through the bony wall of the skull, the primary peripheral focus of inflammation was situated in the nasal cavity or in one of the nasal accessory air sinuses. It is necessary, therefore, to deal briefly with certain aspects of the anatomy of these parts, and especially to define their general relationship to the cranial cavity. In doing so in the following paragraphs, the writer has quoted freely from The Accessory Sinuses of the Nose by A. Logan Turner.

The Nasal Cavities (Fig. 47).- The only part of the nasal cavity which comes directly into intimate relationship with the cranial cavity is that portion of the roof formed by the cribriform plate of the ethmoid. This plate of bone lies horizontally and

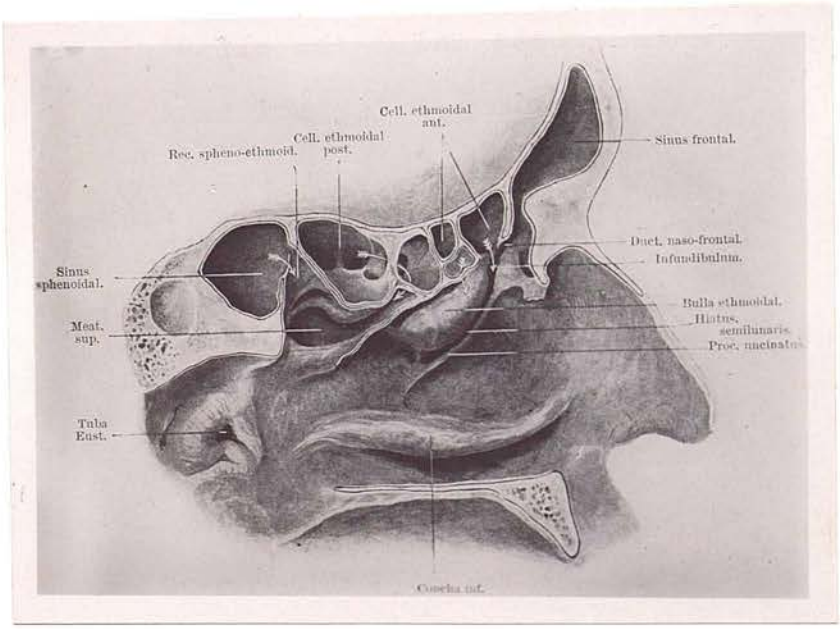


Fig.48.- Reproduced by kind permission of Dr A. Logan Turner from <u>The Accessory Sinuses of the Nose</u>. The illustration shows the higher air cavities on the left side and the lateral wall of the left nasal cavity after removal of the concha superior and concha media. The communications of the air cells with the nasal cavity are seen.

To face page 196.

is very thin; it connects the labyrinthi ethmoidales with the vertical plate; its upper surface forms on either side of the crista galli the olfactory grooves; the bone is covered by dura mater and in the grooves lie the olfactory lobes of the cerebrum, one on each side of the crista. In many instances the olfactory groove is shallow, but not infrequently, as in Fig.47 it is a deep and narrow cleft. In the latter case, the roof of the nose is considerably lower than in the case of a shallow olfactory groove and its clinical importance in relation to operations in the nose and nasal accessory sinuses is obvious, especially if the operation involves the upper regions of the nasal cavity.

The Ethmoidal Cell Labyrinth (Figs.47 and 48).-The medial wall of the labyrinthus ethmoidalis (lateral mass of the ethmoid) enters into the formation of the lateral wall of the nose; the lateral wall of the ethmoidal labyrinth - the lamina papyracea (os planum) - forms the greater part of the medial wall of the orbit. The labyrinthus ethmoidalis is composed of exceedingly thin bone enclosing a varying number of air cells. Anatomically and clinically, these cells may be divided into two groups, anterior and posterior. The two cells groups are separated completely from each

other by a plate of bone placed diagonally between the lateral and medial walls of the labyrinthus ethmoidalis. In some cases the cells comprising the posterior group communicate with the superior meatus by separate ostia; in other cases they are separated from each other by incomplete septa and a single ostium serves as a common orifice for the whole group. The anterior group, on the other hand, usually communicate with the middle meatus by several ostia.

While the air spaces are closed laterally chiefly by the lamina papyracea and medially chiefly by the lateral wall of the nasal cavity, the remaining four boundaries are formed by bones other than the ethmoid. Of these, however, only the superior wall is of importance to the present subject; here the cells are completed by the ethmoidal edge of the orbital plate of the frontal bone.

Not uncommonly one of the air cells of the anterior group develops upwards and forwards towards the frontal air sinus and forms a distinct prominence upon its floor and in this case the bony partition between the ethmoidal cell and frontal sinus is very thin. Again, one of the anterior ethmoidal cells not infrequently pushes its way outwards behind or beneath the frontal sinus for a considerable distance

Fig.49.- Drawing of a specimen kindly lent to the author by Dr. A. Logan Turner to illustrate direct extension of infection through the orbital roof. The patient, a girl, aged 14, developed acute rhinitis with suppuration in the higher air sinuses on the left side. The left orbital roof showed patches of cario-necrosis and in its centre was a small circular perforation with a corresponding perforation in the dura mater lying over it (indicated by a quill). Adhesions had formed in the pia-arachnoid membrane around the aperture and in the left frontal lobe an abscess had developed (see Fig.50). The duration of the illness was five weeks.

To face page 198.

between the two tables of the orbital plate of the frontal bone and may extend as far back as the optic foramen (Logan Turner).

Variations of the posterior group of ethmoidal air cells also occur. Thus, one of the posterior cells may project for a considerable distance into the body and lesser wing of the sphenoid bone and thus intervene between the sphenoidal air sinus and the basis cranii.

Not only do the bony partitions between the ethmoidal air cells themselves consist of extremely thin plates, but the laminae between the various ethmoidal border cells and the frontal, maxillary and sphenoidal air sinuses are also very thin. This relationship of the ethmoidal air cells to each other and their relationship to the other nasal accessory air cavities is of importance since caries of the laminae, followed by perforation, may occur in the course of chronic suppuration with consequent infection of a neighbouring air cavity.

The relationship of the lateral wall of the ethmoidal cell labyrinth to the orbital cavity is also of importance. Chronic suppuration in the ethmoidal air cells may cause perforation of the thin lamina papyracea with subsequent extension of the

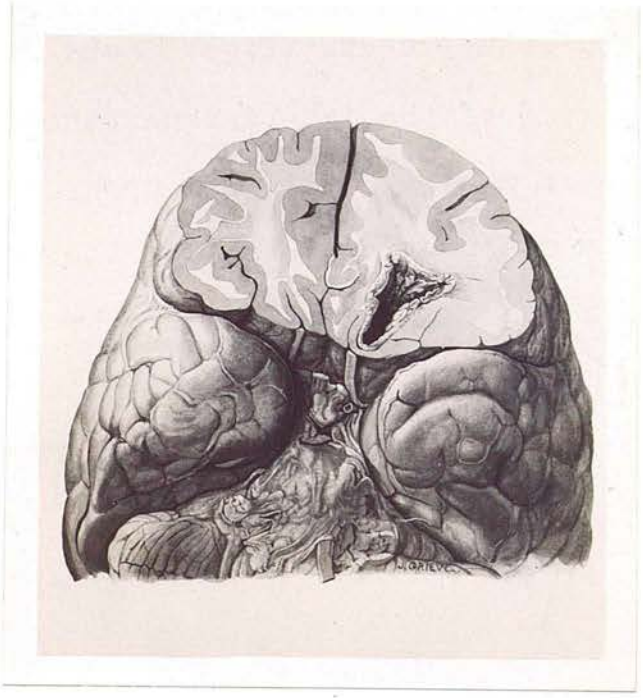


Fig.50.- Photograph of a drawing of a coronal section through the frontal lobes of the same case from which Fig.49 is taken. It shows the abscess in the left frontal lobe.
(Case of H.N., published in Edin. Med. Journ., 1909, New Series, Vol. II., p.432.)

To face page 199.

inflammatory process into the orbital tissues (See Cases VI, X and XI). Thence infection of the intracranial structures may occur (Figs. 49 and 50).

The bony roof of the labyrinthus ethmoidalis is extremely thin in many places; its upper surface is covered by dura mater and enters into the formation of the anterior cranial fossa. The ethmoidal air cells are thus in close contiguity with the inferior surface of the frontal lobes of the cerebrum and their overlying membranes. Should a posterior ethmoidal cell project backwards into the body or lesser wing of the sphenoid bone, its relationship to the intracranial structures is that of the sphenoidal cavity as ordinarily obtaining.

The Sphenoidal Sinuses (Figs. 48 and 51).- The size of the sphenoidal cavity is subject to a certain amount of variation in different individuals, and inequality in its dimensions on the two sides of the same individual is frequent. Thus, the cavities may be limited to the anterior part of the body of the bone or may reach as far as and even into the basi-occipital behind, and extend laterally into the bases of the great wings and superiorly into the lesser wings of the sphenoid bone. Naturally, the larger the size of the cavity, the thinner are its walls and

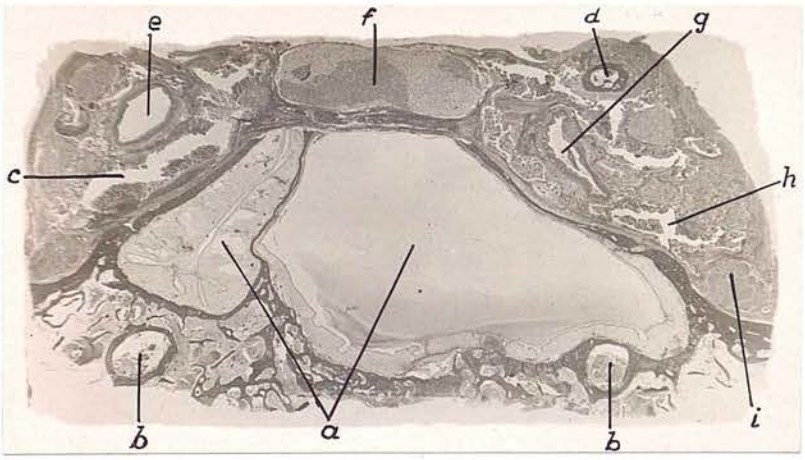


Fig.51.- Photograph of a preparation cut in the coronal plane through the middle of the pituitary body; the relationship of the sphenoidal air sinuses to the intracranial structures is shown (X 2·4 diameter).

a. Right and left sphenoidal sinuses

b. Pterygoid (Vidian) canal

c. Right cavernous sinus

d. Anterior clinoid processes

e. Right internal carotid artery

f. Pituitary body

g. Left internal carotid artery

h. Left cavernous sinus

i. Maxillary division of cranial nerve V.

To face page 200.

the closer is it to the intracranial structures.

The roof and posterior part of the lateral wall enter into the formation of the middle cranial fossa. They are usually thin, are covered by dura mater and possess a close relation to many important intracranial structures. The roof is in relationship to the olfactory tract, the optic chiasma, the pituitary body, and the pons Varolii. At the junction of the roof with the lateral wall, the optic nerve and ophthalmic artery pass forward to the orbit. The lateral wall is in relation to the internal carotid artery and the cavernous blood sinus; anteriorly it forms the medial boundary of the superior orbital fissure and is thus in relation to the third, fourth, ophthalmic division of the fifth, and sixth cranial nerves, and to the ophthalmic veins. The lateral portion of the anterior wall of the air cavity is thin and articulates with the posterior part of the labyrinthus ethmoidalis completing the ethmoidal cell labyrinth in this situation; thus it is in relation with the posterior group of ethmoidal air cells.

The Frontal Air Sinuses (Figs.48,52, and 53).- The frontal air sinuses extend vertically upwards for a varying distance, and in many instances horizontally backwards, between the two tables of the orbital

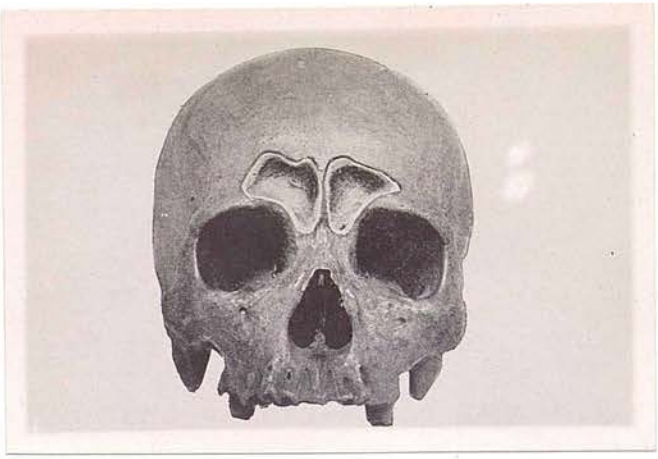


Fig.52.- Reproduced by kind permission of Dr A. Logan Turner from The Accessory Sinuses of the Nose. Frontal sinuses of average dimensions.

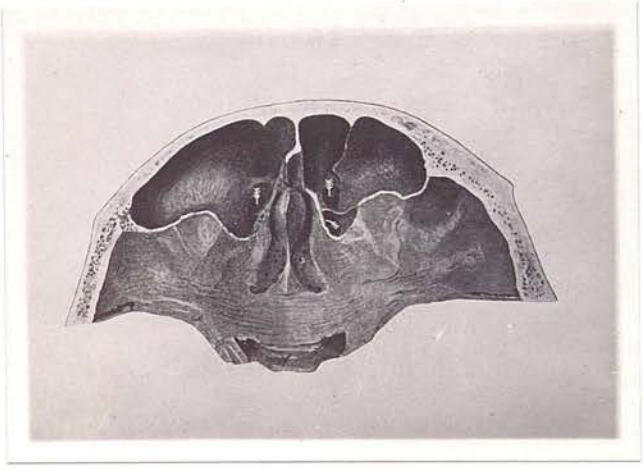


Fig.53.- Reproduced by kind permission of Dr A. Logan Turner from The Accessory Sinuses of the Nose. Floor of the anterior cranial fossa. The orbital portion of each frontal air sinus is opened into from above, and the position of the ostium of each cavity is indicated by an arrow; both openings are situated posteriorly in this case. Behind the right frontal sinus an ethmoidal cell is seen, the arrow indicating its communication with the nasal cavity.

To face page 201.

plate. Laterally, the cavity may extend as far as the processus zygomaticus (lateral angular process) of the frontal bone and occasionally it has been found to extend as far backwards as the optic foramen.

The posterior wall is formed by the inner table of the vertical part of the frontal bone; it varies in thickness and not infrequently portions of it are extremely thin. It enters into the formation of the anterior cranial fossa and is in relation therefore to the frontal lobe of the cerebrum and the membranes overlying it.

The inferior wall or floor is the thinnest of the three walls and is formed by the lower of the two bony laminae which make up the orbital plate of the frontal bones. Its lateral portion corresponds mainly to the medial third of the roof of the orbit and its medial portion is in close relationship with the ethmoidal cell labyrinth.

The septum is thin and in a series of 578 crania examined by Logan Turner it was never found incomplete in the normal skull. Deviation of the septum to one or other side is not infrequent and is due probably to the more rapid development of one of the sinuses. The obliquity may be so pronounced that suppuration in one sinus may cause direct infection of the brain

on both sides of the mesial plane.

The Maxillary Sinus.- Most authorities are agreed that in those cases in which the maxillary sinus has been regarded as the direct origin of an intracranial infection, an associated septic focus in one of the higher air cavities is more probably the source of the infection (see Case XII, p.174). Hence, for the purpose of this Thesis, a consideration of the anatomy of the maxillary sinus is not required.

In the majority of recorded cases in which infection has spread by direct extension through the bone and into the dura mater, the primary complication has been a leptomeningitis. In a certain number of instances, however, the spread of the infection from the initial focus has begun by direct extension through bone and then passed by the venous blood stream to the cavernous sinus causing there a septic thrombosis. The present Series of cases contains three examples of this sequence in the course of the extension of infection (Cases VI, X, and XI).

Again, if the supero-lateral bony wall of the sphenoidal air sinus be the site of cario-necrosis,

the dural wall of the cavernous blood sinus may be implicated by direct extension of the inflammatory process with consequent thrombosis of the cavernous spaces. Case XIV is an example of this.

CASE XIV. Acute Suppuration in the Accessory Air Sinuses: Cavernous Sinus Thrombosis: Acute Leptomeningitis: Death: Autopsy.

This case illustrates infection of the leptomeninges, brain and cavernous blood sinus by direct extension through the bone from a primary focus of inflammation in the nasal accessory air sinuses.

E. A., aged 29, housewife, was admitted to the Ear and Throat Department, Royal Infirmary, on 20th March, 1925, under the care of Dr J.S. Fraser, F.R.C.S.E., to whom I am indebted for the following clinical notes.

The patient complained of bilateral nasal obstruction, which she attributed to a severe cold three weeks previously. No history was obtained as to nasal trouble of longer duration. A considerable quantity of thick discharge came from the nose. She did not suffer from headaches. The patient also stated that she had suffered from toothache in the molar region of the left upper jaw and had had an abscess in her mouth; a dentist had extracted teeth.

On admission, the soft palate and posterior part of the alveolus on the left side were covered with a

thick, white pseudo-membranous exudate. The patient was sent to the Dental Department where Dr J.H. Gibbs recommended antiseptic treatment to the inflamed gums. This was carried out, the patient being confined to bed.

On 1st April, as the condition showed no improvement, both maxillary sinuses were punctured and pus was washed out. Swabs were also taken from the throat and from the nasal cavities and examined by Dr W.R. Logan who reported as follows:-

"The nasal cavity.- Films showed fusiform bacilli of Vincent's type, but no spirochaetes were present; there were a few Gram-positive diplococci. Cultures produced cocci of the pneumococcal and streptococcal groups. No diphtheria bacilli were found."

"The throat.- Gram-positive cocci and long Gram-positive bacilli were seen in films; there were no Vincent's fusiform bacilli or spirochaetes and no diphtheria bacilli. On culture the great majority of the colonies were staphlococcal."

Wassermann's test gave a negative result.

On 8th April the eyes were examined as the patient had developed slight oedema of the right upper eyelid. Dr A.H. Sinclair found the pupils normal and no proptosis; the movements of the eyeballs were

unrestricted; vision was 6/12 in both eyes and the optic discs showed no changes.

X-ray plates showed some opacity of all the paranasal sinuses.

On 14th April, six days later, slight proptosis of the right eyeball was present; the oedema of the right upper eyelid had disappeared. There was no orbital pain or tenderness.

On 15th April, the right eyeball had become immobile and the right pupil was larger than the left and in a condition of stabile mydriasis. The patient did not complain of headache.

During the night of the 15th she developed fits; these commenced suddenly without warning; she became unconscious.

On 16th April there were intervals of partial consciousness, during which she answered questions. No further fits were observed.

On 17th April the patient died at 4.30 a.m.

The following brief summary of the temperature chart is of interest. During the first seven days after admission to hospital, 27th March to 2nd April, the temperature varied from 98°F. to 100·2°F., and between the latter date and the 12th April, with the exception of the 10th and 11th, the evening

Case XIV.

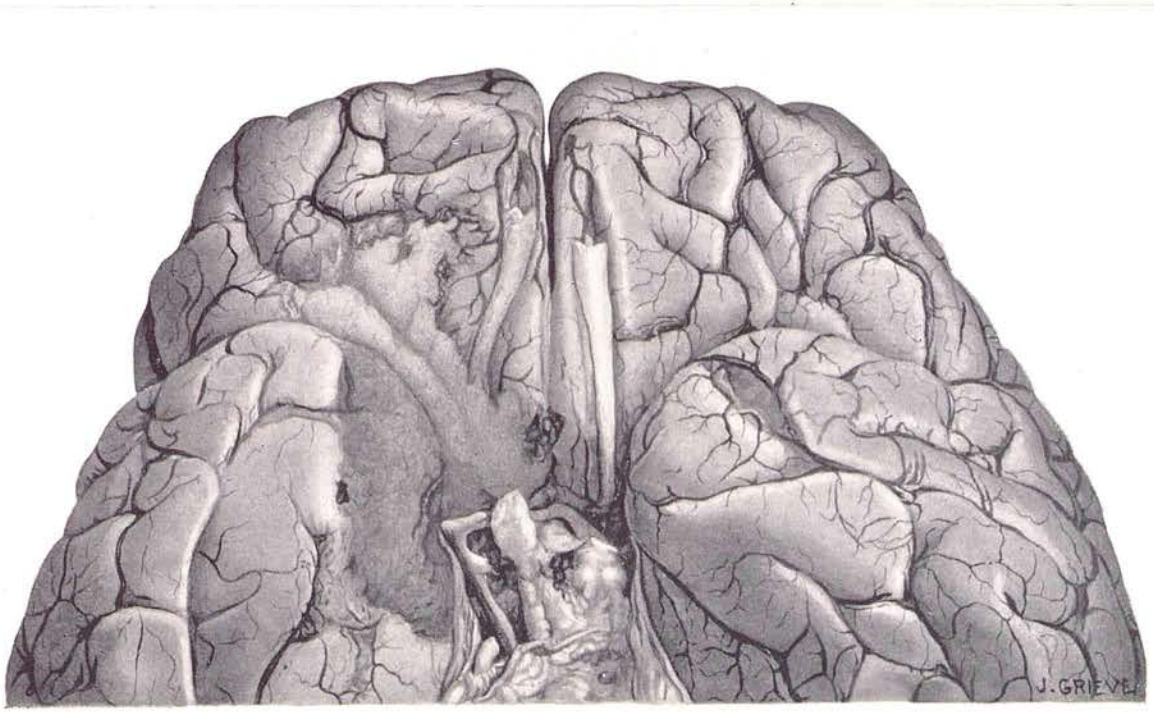


Fig.54.- The illustration shows the inferior surface of the anterior part of the cerebrum. The antero-medial portion of the right temporal lobe is necrotic. Pus is present in the interpeduncular space and extends forwards on to the inferior surface of the right frontal lobe and right olfactory tract. On the same side the convolutions are flattened.

To face page 207.

temperature varied from 100·6°F. to 102.2°F. From the 12th April to her death on the 17th, the general trend of the temperature was higher, reaching 103.4°F. on more than one occasion, finally, just before death, registering 105·2°F. The last period coincided with the onset and progress of leptomeningitis.

Autopsy.- This was performed on the head only, seven hours after death. Diffuse purulent leptomeningitis was present on the base of the brain, being specially marked in the area of the pituitary body. The medial border of the inferior surface of the right temporal lobe was of a dirty, blackish-grey colour and gangrenous: the condition extended almost to the tip of the lobe (Fig.54). The adjacent portion of the right frontal lobe showed a similar though less pronounced change; there was considerable purulent infiltration of the leptomeninges in the same region, the infiltration extending forwards along the olfactory tract. The right optic nerve was swollen, and of softer consistence than the left, which was firm and of normal contour. The meningeal vessels on the right hemisphere of the brain were congested and the convolutions somewhat flattened. On the left side of the brain, none of the above changes were present (Fig. 54).

On the base of the skull the right half of the pituitary body was in parts of a dirty-grey almost black discoloration due to gangrene, and pus lay anterior to it. The portions of dura mater forming the lateral wall of the right cavernous blood sinus, covering the lesser wing of the sphenoid and the floor of the middle fossa on the same side were of a similar greyish-black colour; the dura mater in the latter situation was raised from the adjacent body of the sphenoid by a small accumulation of pus.

On the left side the pituitary body and dura mater did not show these changes.

The right frontal sinus contained pus; the left sinus was absent. Both maxillary sinuses were the seat of purulent inflammation. The ethmoidal and sphenoidal air-cells were not opened at autopsy, a block of bone containing them being removed for further examination. The block also comprised the structures in the pterygoid fossa, the posterior part of the nasal cavities and the hard and soft palates.

The following points were observed on examination of the specimen. On the right side the orbital contents and the ethmoidal air-cells were in great part destroyed and presented a softened appearance due to purulent infiltration. On the left side the

ethmoidal cells and the structures in the orbit were intact.

Direct films from the pus on the base of the brain showed numerous staphylococci and diphtheroid bacilli. Cultures gave a scanty growth of staphylococci.

Report on the Material examined Microscopically.

The Posterior Ethmoidal Cells.- On the right side, in one large ethmoidal cell, the lining columnar epithelium, with the exception of a small area on the roof, was desquamated. The denuded superficial layers of the mucous membrane on the medial wall of this cell were necrotic; the deeper parts were swollen, oedematous, and densely infiltrated by mononucleated cells and polymorphonuclear leucocytes. The cavity of the air-cell contained granular necrotic material. In a portion of another cell lying lateral to and above the former, the lining columnar epithelium was intact, and the subepithelial tissues showed little change. The air space contained mucus. The only remaining part of the osseous wall was a small portion contiguous to the roof of an air-cell and seen in some of the sections of the series. The periosteum had been stripped both from the medial and lateral surfaces and the bone was in process of

absorption.

In the left ethmoidal cells the only pathological change consisted in an oedematous swelling and cellular infiltration of the mucous membrane.

The Sphenoidal Air Sinuses.- The mucous membrane covering the upper and lateral wall of the right sphenoidal sinus was necrosed and had in part disappeared. On the floor and medial wall the mucosa was inflamed and densely infiltrated by pus, while its superficial layers showed various stages of necrosis. The air cavity itself contained a large amount of purulent and necrotic material.

The lateral bony wall of the right air sinus with the contained diploë was necrotic, the change being most pronounced in the upper part of this wall. There was complete absence of reaction on the part of the bone marrow in the area adjacent to the necrosis (Fig.56). In the diploë of the medial portion of the roof, many of the veins were thrombosed, in some the clot being septic. Further, infective changes were widespread in the bone marrow of the body of the sphenoid and extended downwards into the base of the pterygoid processes.

The medial wall (the intersinus septum) was very thin and contained no diploic tissue; it showed

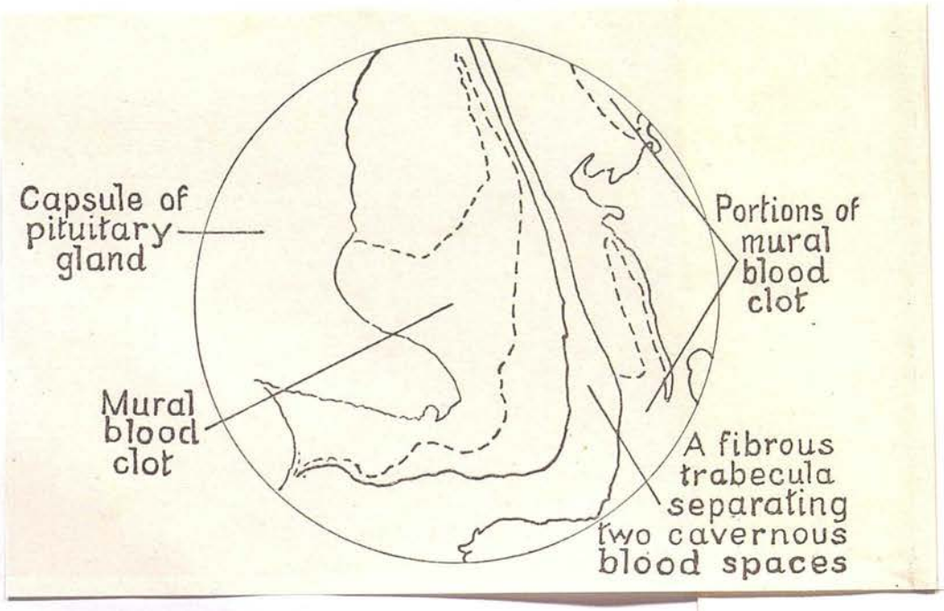
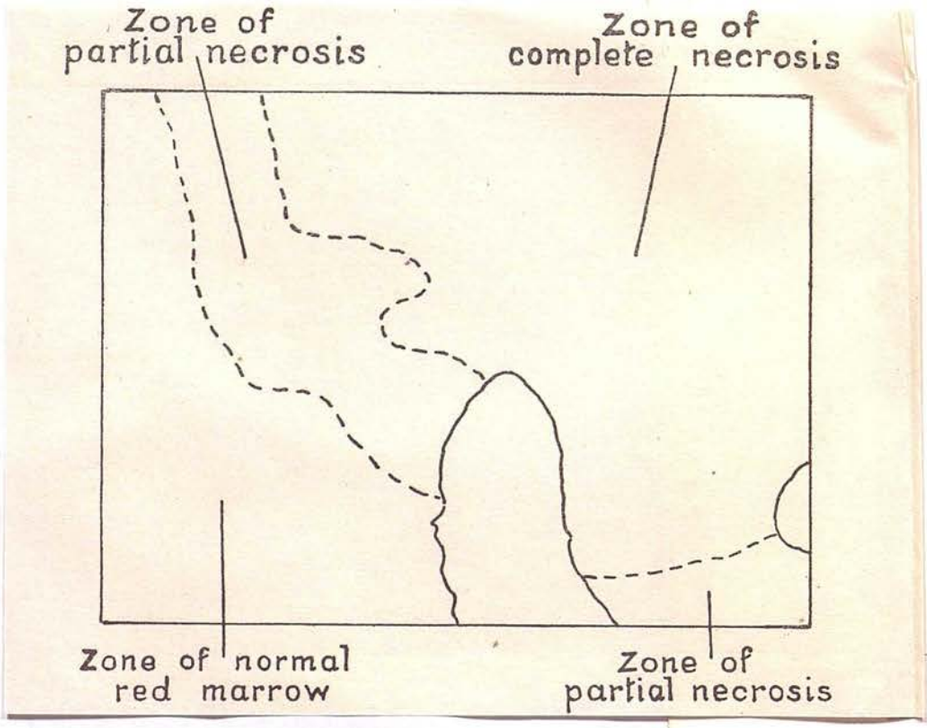


Fig.55.- Portion of the left cavernous blood sinus: the blood clots have a mural attachment and only partially fill the blood spaces. The clots show early infection. (L.P.)



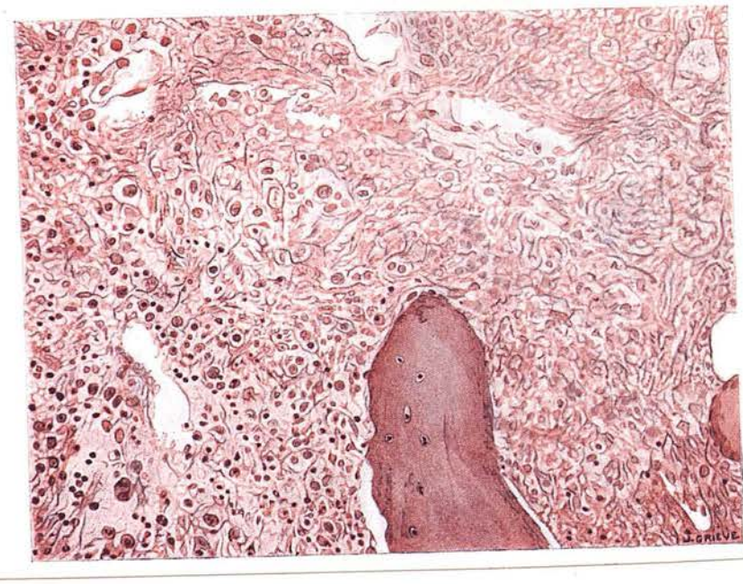


Fig.56.- Portion of the lateral wall of the right sphenoidal air sinus. There is necrotic (right) and normal (left) bone-marrow. The latter shows no reaction. (H.P.)

To face page 211.

numerous small dehiscences. There was considerable osteoclastic activity in relation to the inflamed lining membrane of the right air sinus.

In the left sphenoidal air sinus the mucous membrane on the medial (septal) wall was inflamed and a portion of it was necrotic. Elsewhere in the sinus the lining mucosa presented little change. The bone and the bone marrow in the lateral walls of the sinus showed no pathological changes.

In both Vidian (pterygoid) canals the small veins were not thrombosed, but the connective tissue in the canals was infiltrated by cells; most of these were mononucleated in type, although a few polymorphonuclear leucocytes were present on the right side. The cellular infiltration was most dense round the small veins.

The Cavernous Blood Sinuses.- On the right side the site of many of the pre-existing blood spaces of the cavernous sinus and of the surrounding connective tissue was occupied by necrotic material. The blood spaces still remaining contained disintegrating blood clot.

The nerve bundles in the lateral wall of the cavernous blood sinus were neither necrotic nor infiltrated by pus, the perineurium of the bundles

remaining intact; the lateral portion of the right Gasserian ganglion, however, was necrotic. Nearly the whole of the right half of the pituitary body had also undergone necrotic changes.

On the left side the cavernous blood spaces persisted; some of them, however, showed early septic thrombosis. Certain of the clots had a mural attachment and did not completely fill the blood space (Fig. 55). The wall of the sinus to which the early thrombi were attached, along with the neighbouring connective tissue, was infiltrated by polymorphonuclear leucocytes and mononucleated cells.

The inferior portion of the circular sinus contained disintegrated material.

Nasopharynx and Soft Palate.- The mucous membrane on the roof of the nasopharynx showed intense inflammation and purulent infiltration. The buccal mucosa covering the soft palate was ulcerated and necrotic.

Commentary.

From the appearances described above, it is clear that the case illustrated infection of the intracranial structures by direct extension through the bone from a peripheral focus of inflammation in

the nasal accessory air-sinuses. In the right ethmoidal area a purulent necrosing osteomyelitis had caused an almost complete disappearance of the orbito-ethmoidal wall and destruction of a considerable part of the orbital contents. In a similar manner in the right sphenoidal region the inflammatory process had extended upwards and laterally from the air cavity into the middle cranial fossa, giving rise to an extensive extradural abscess, and to necrosis of the dura mater including the portion forming the walls of the right cavernous blood sinus. As a result of this, thrombosis occurred within the lumen of the blood sinus; the clot became infected and disintegrated. Further, the necrosis involved the right half of the pituitary body and, on the same side, the lateral portion of the Gasserian ganglion, and the antero-medial part of the temporal lobe.

Speaking generally, in every case the type of inflammation depends upon the reaction of the tissues in response to the irritant. In the present instance the reaction of the tissues was minimal to the staphylococci responsible for the intracranial complication. The slight response to the various micro-organisms which gave rise to the changes in the palate and fauces had a similar influence on the type

of the inflammatory process in these structures. In all situations the process was essentially similar, namely, a slowly advancing necrosis.

Among the interesting features of the present case is the manner in which the infective process was localised. As has been noted and illustrated (Fig. 56), a sharp line of demarcation existed between the living and the dead tissue; the necrosed indicated the path of infection between the primary focus in the ethmoidal and sphenoidal regions and the intracranial contents. In other words, although extension of the process occurred, this case is an example of focal infection.

If the explanation of the focal nature of the spread of the infection could be given, it would account for the absence of reaction on the part of the tissues immediately adjacent to the necrotic material and for the comparatively long course of the disease.

So little is understood, however, of the factors underlying focal as opposed to diffuse infection, that a precise explanation of these phenomena cannot be stated. In this connection, among determining factors, the antibacterial and antitoxic properties of each individual probably play an important part.

It seems to the writer that the present case is to be considered as one in which the antibacterial factors were predominant, keeping the micro-organisms under control and preventing them becoming widespread in the tissues. On the other hand, the antitoxic properties of the body were deficient, and therefore the patient showed the usual manifestations of general toxaemia.

CASE XV. Catarrhal Ethmoiditis: Nasal Polypi: Radical Operation on the Ethmoidal Air Cells: Acute Leptomeningitis: Death: Autopsy.

This case is an example of acute purulent leptomeningitis due to infection passing directly from the nasal cavity to the leptomeninges through an aperture in the cribriform plate resulting from operative trauma.

M. R., female, aged 41.

In 1922, the patient was admitted to a general Medical Ward of the Royal Infirmary, Edinburgh, suffering from asthma. As she also complained of nasal catarrh and pain in the left cheek, she was examined in the Ear and Throat Department, but no paranasal sinus disease was detected at that time.

In January 1924, the patient was again examined by a rhinologist and a small polypus was seen in the right nasal cavity.

By March 1925, the nasal symptoms had become aggravated. The mucosa of both middle conchae was now very oedematous and a polypus was present in the left nasal cavity. A skiagram demonstrated a normal condition of the maxillary sinuses, blurring of the

Case XV.

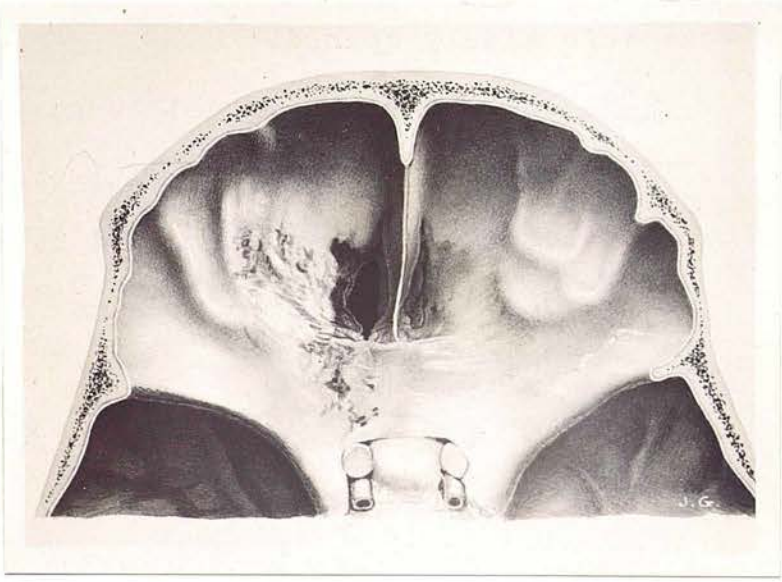


Fig.57.- Photograph of a drawing showing the aperture in the cribriform plate on the left side due to operative trauma. A thin layer of clotted blood covers the dura mater in the immediate neighbourhood of the aperture and small blood stained areas are visible on the orbital plate and small wing of the sphenoid bone.

To face page 217.

ethmoidal cells and an absence of frontal sinuses. The middle conchae were removed and both the ethmoidal labyrinths were widely opened.

In May 1928, the patient returned to hospital complaining of nasal obstruction especially on the left side. Both nasal cavities contained polypi, but a skiagram showed no blurring of the maxillary sinuses.

On 12th May, the polypi were removed and the ethmoidal cells were further dealt with. On the afternoon of 13th May, the patient complained of headache, and during the night 13th/14th May she became very restless and slightly delirious. Signs of leptomeningitis developed; she gradually became comatose and died at 10 p.m. on 15th May.

Autopsy.- Permission was obtained to examine the head only. A well marked acute purulent leptomeningitis was present over the whole cerebrum and base of the brain. A large defect was found in the posterior part of the cribriform plate on the left side and in the overlying dura mater. A thin layer of clotted blood covered the cerebral surface of the dura mater in the immediate neighbourhood of the aperture, and small blood stained areas were visible on the orbital plate and small wing of the sphenoid bone (Fig.57).

The aperture measured 1·5 cm. antero-porteriorly and its greatest transverse measurement was 6 mm.; the edges were thin and rather irregular in outline. Through the opening, blood clot was visible in the nasal cavity.

Bacteriology.- On culture, the pus from the leptomeninges yielded a pure growth of a haemolytic streptococcus.

Microscopical Examination of the Cribriform Plate on the Left Side.- Serial sections made in the coronal plane showed that the bony margins of the aperture were sharp and posteriorly that the fracture had occurred between two of the cribriform openings. In this neighbourhood the aperture was partly occupied by a piece of subepithelial nasal tissue and by a strip of torn dura mater. There were also several small spicules of bone in the aperture.

On the medial side, there was a spicule of bone which had not been completely detached from the cribriform plate.

The bone forming the margin of the aperture was not necrosed and the Haversian canals in the neighbourhood were not infected.

In the nasal mucosa distant from the aperture there were haemorrhages resulting from operative

trauma.

Summary.- During operation on the left nasal cavity and ethmoidal air cells, a portion of the cribriform plate of the ethmoid with the overlying dura mater was inadvertently removed. Through the opening, infection passed from the nasal cavity to the leptomeninges; signs of acute leptomeningitis occurred some 36 hours after the operation and the patient died of generalised acute purulent leptomeningitis three and a half days after operation.

CASE XVI. Acute Inflammation of the Higher Accessory Air Sinuses: Leptomeningitis: Operation: Death: Autopsy.

A.S., male, aged 19, was admitted on 22nd March, 1929, to the Ear and Throat Department, Royal Infirmary, Edinburgh, under the charge of Dr J. S. Fraser, F.R.C.S.E., to whom I am indebted for the following clinical notes.

Three weeks before admission the patient had an attack of influenza associated with considerable nasal discharge. He had been ill ever since.

One week before admission he suffered from pain above both eyes; the pain was constant and it was associated with swelling in the lower part of the forehead.

On 22nd March, when admitted to hospital, in addition to the pain above the eyes, the patient complained of pain in the back of the head. He was somewhat drowsy and looked ill. The temperature was 104°F. and the pulse rate 112. The soft tissues over the lower part of the forehead and especially over the glabella were puffy. The upper and lower eyelids on both sides were oedematous and there was great

tenderness on pressure upon the floor of each frontal sinus.

On anterior rhinoscopy a considerable quantity of thick yellowish white pus was seen in both nasal cavities and, on posterior rhinoscopy, behind the soft palate. The tongue was furred and the breath had an unpleasant odour. Both ears were normal. The patient was too ill for X-ray examination to be carried out.

Operation was performed under a general anaesthetic soon after the patient was admitted to hospital. Both frontal sinuses were opened through external incisions. Pus was found beneath the periosteum over the glabella, in which situation an erosion existed in the anterior wall of the right frontal sinus.

Foul-smelling pus was present in both frontal sinuses and perforation of the intersinus septum had occurred. Their mucous membrane was necrotic and was easily removed. The bone forming the posterior wall of each sinus was unduly white.

The anterior wall and the floor of both sinuses were removed; the ethmoidal cells on both sides and the sphenoidal sinuses contained pus and were therefore opened.

At the operation, a lumbar puncture was performed. Clear cerebrospinal fluid was obtained; the cells were 3 per c.mm. and a trace of globulin was present.

On 23rd March, the patient's condition had improved; the tongue was moist and the temperature 102°F.

On 24th March, it was reported that he had passed a very restless night and had become unconscious in the early morning. Death occurred at noon.

Autopsy.- Permission was obtained to examine the head only and this was done 24 hours after death.

The leptomeninges covering the right hemisphere from its vertex to base contained a large amount of foul-smelling pus. Over the left hemisphere they were greatly congested but no pus was seen. No brain abscess was present, and there was no antemortem thrombus in the dural blood sinuses or pus in the middle ear on either side.

Bacteriology.- 1. From the pus in the frontal sinus taken at operation, a growth of a non-haemolytic streptococcus was obtained.

2. Direct films of the pus in the leptomeninges taken at autopsy showed small Gram-positive lanceolate diplococci, probably Pneumococcus, and small Gram-

negative bacilli corresponding in morphological type to Bacillus influenzae, Pfeiffer. Blood agar, coagulated blood and citrated blood agar were inoculated by the pus, but no growth had occurred after 48 hours incubation.

Preparation of the Material for Microscopic Examination.- Before removing the brain, the anterior portions of the frontal lobes were cut off and left in situ. These along with the adjacent leptomeninges, dura mater, and posterior wall of the frontal sinuses were removed in one block. This was placed in Parenny's solution and after decalcification of the bone was complete, the block was mounted in gelatine to keep the parts in apposition. It was then divided in the sagittal plane into portions suitable for embedding in paraffin.

Report on the Material examined Microscopically.

1. The remains of the mucous membrane of the frontal air sinuses was necrotic and infiltrated by pus.

2. The posterior bony wall of the frontal air sinuses.- The layer of bone next the air cavity was for the most part necrotic and was being absorbed; small sequestra had been detached from its surface. The structural elements of some of the Haversian

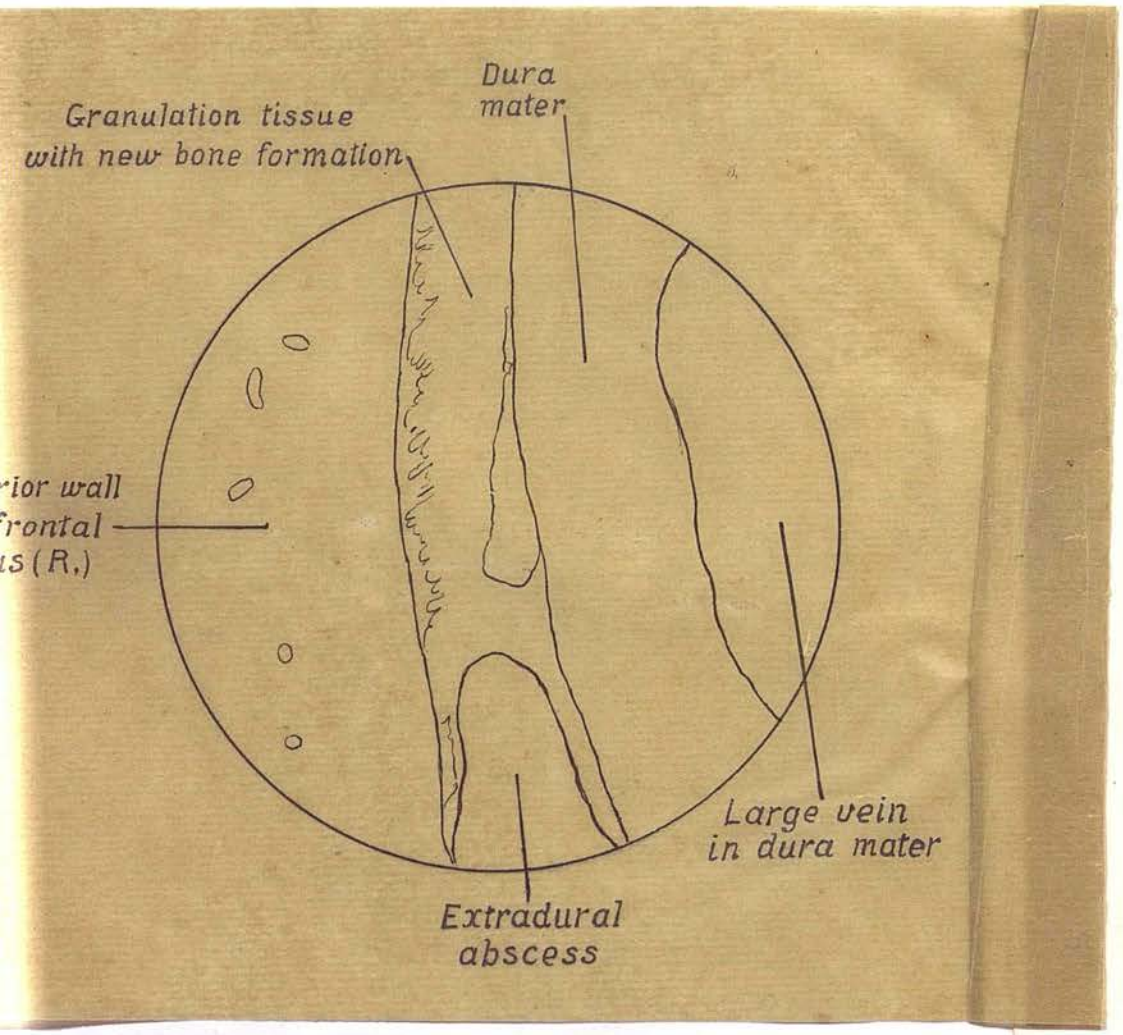


Fig.58.- Sagittal section through the right lateral portion of the extradural abscess. The upper wall is formed of granulation tissue in which new bone is being laid down.
(Stained by haematin and eosin.)

To face page 224.

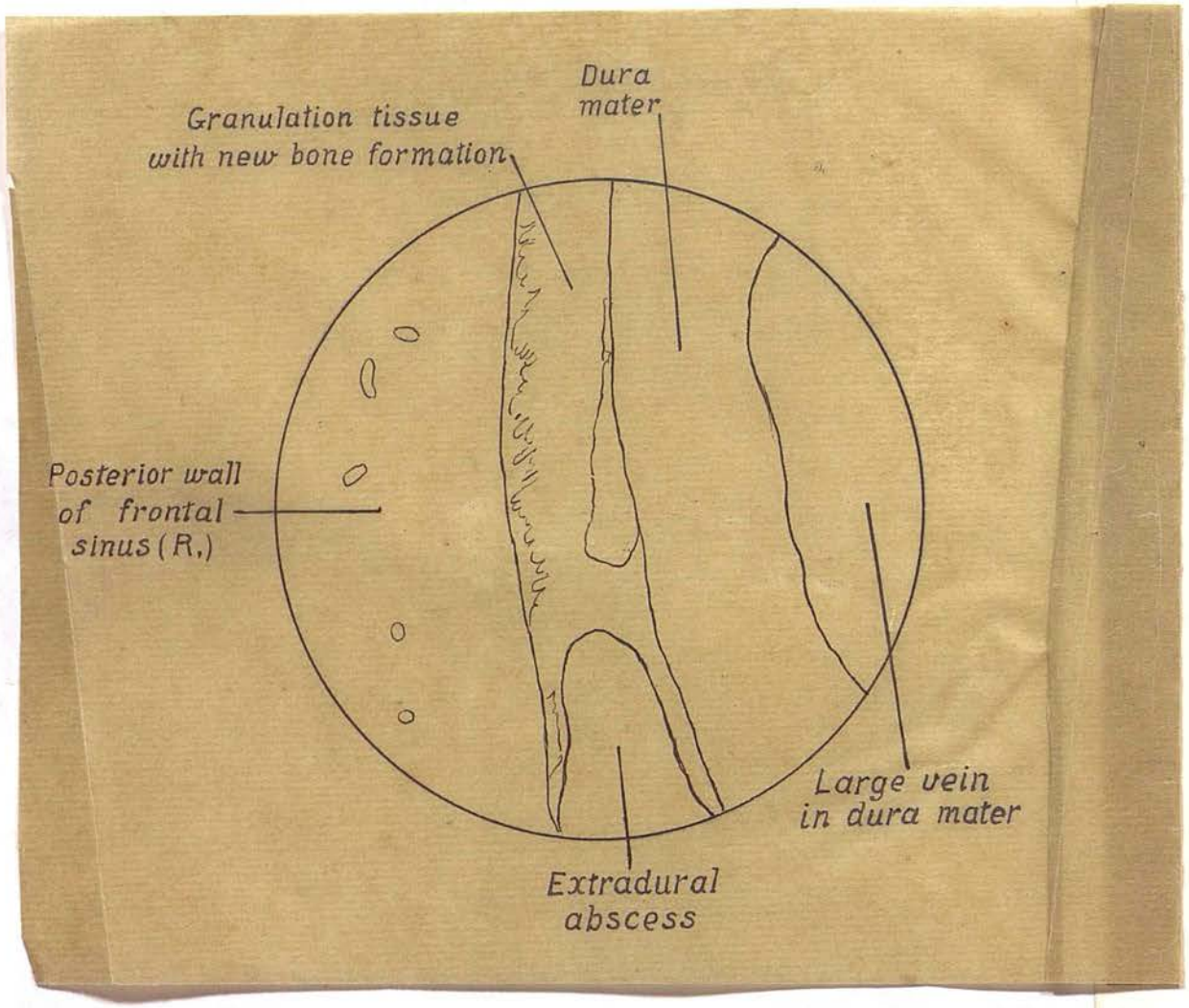


Fig.58.- Sagittal section through the right lateral portion of the extradural abscess. The upper wall is formed of granulation tissue in which new bone is being laid down.
(Stained by haematin and eosin.)

To face page 224.

canals had disappeared completely and the canals were full of pus.

In the deeper parts of the bone, osteoclastic activity was marked in the Haversian canals. The diploë had disappeared from some of the marrow spaces which were full of pus. In other spaces, the marrow contained pus and in several instances diploic veins were filled with septic thrombi; in others again the small blood vessels were dilated, diapedesis of polymorphonuclear leucocytes through their walls was active and the surrounding diploë was infiltrated by this type of cell.

3. Extradural abscess.- Between the bone and dura mater an abscess had formed, extending behind both frontal sinuses; the larger collection of pus was behind the right sinus. Along the superior wall of the abscess, especially in its right lateral portion, granulation tissue had been formed and in this, new bone was being laid down (Fig.58).

4. The dura mater.- The dura mater adjacent to the extradural abscess was densely infiltrated by polymorphonuclear leucocytes, particularly behind the lateral third of the right sinus. The infiltration was most marked in the middle and inner layers of the dural membrane; serial sections demonstrated an area

in which the pus in the extradural abscess was continuous with the purulent infiltration in the dural layers.

5. The leptomeninges.- The leptomeninges were infiltrated by pus and this again was continuous with that in the dural layers. None of the veins in the leptomeninges were thrombosed.

Commentary.

In this case, about three weeks before death the patient suffered from influenza and acute nasal catarrh. At this time, all the higher nasal accessory air sinuses became infected. The suppuration in the frontal sinuses not only caused necrosis of the lining mucous membrane but also passed into the bone. Cario-necrosis of the anterior wall of the right sinus led to erosion and two weeks after the initial onset of the disease, a subperiosteal abscess formed over the glabella. Perforation of the intersinus septum also occurred. The bone forming the posterior wall of the frontal sinuses became infiltrated by pus and considerable areas of its subjacent portion became necrotic. An extradural abscess formed; the infection proceeded from here to infiltrate the layers of the dura mater and finally reached the pia-arachnoid spaces. In the absence

of adhesions between the cerebral surface and the dura mater here - nature's attempt to localise the infection - an acute spreading purulent leptomeningitis supervened.

In this case, the microscope has fully demonstrated direct extension of infection from the frontal air sinuses through their posterior bony walls and through the underlying dura mater into the leptomeninges.

CASE XVII. Acute Suppuration in Left Frontal Sinus: Right Frontal Lobe Abscess: Operation on Left Frontal Sinus: Death: Autopsy.

R. P., male, aged 27, a miner, was admitted on 16th March 1927 to the General Hospital, Nottingham, under the care of Mr Bell Tawse, F.R.C.S., I am indebted to him and to Dr Gilroy Glass, House Surgeon, for the notes of the case and the pathological material.

The patient had suffered from influenza nine weeks before admission. This was followed in a few days by pain over the left eye accompanied by discharge from the left nostril.

Five weeks after the commencement of the influenza, the left upper and lower eyelids became swollen, but no particular attention was paid to this occurrence.

Two weeks later he became seriously ill and showed considerable cerebral irritability. He was then admitted to a hospital. An incision was made along the left eyebrow and a considerable quantity of pus was evacuated from the orbit, but no further treatment was carried out.

A fortnight later (nine weeks after the commencement of his illness) the patient was transferred to the care of Mr Bell Tawse at the General Hospital. On admission, the patient was in a comatose condition. Oedema extended upwards from the eyelid over the area of the left frontal sinus and pus was exuding from the eyebrow incision. Pus was present in the left middle meatus and left choana.

The right pupil was dilated and did not react to light. The left pupil was of pin-point size. Kernig's sign was present on both sides; the knee-jerks were exaggerated and the plantar reflex was extensor.

The cerebrospinal fluid obtained by lumbar puncture was clear, but under increased pressure; the cells numbered less than 5 per cmm.; albumin 0·06 per cent.; sugar present. Culture media inoculated from the cerebrospinal fluid gave no growth.

Operation was performed immediately after admission. The left frontal sinus was opened and was found to extend across the middle line. The cavity was full of pus under pressure. The cerebral wall was intact and was not interfered with. The coma continued and the patient died thirty-six hours later.

Bacteriological examination of the pus from the

frontal sinus revealed in films a few very small Gram-negative intracellular bacilli; on culture no growth was obtained.

Autopsy.- Only one frontal sinus was present, namely the left. The cavity, which lay mainly over the left eye, extended across the middle line and approximated the inner third of the right supra-orbital margin; an incomplete partition subdivided the sinus into a large left and smaller right portion. A small ethmoidal cell extended into the roof of the right orbit and lay beneath the extension of the frontal sinus on the right side.

On removal of the brain, no leptomeningitis was seen. At one small area on the anterior surface of the right frontal lobe and behind the frontal sinus area the surface of the brain was adherent to the dura mater. Immediately behind this area there was a large frontal lobe abscess containing from 3 to 4 ounces of pus.

The dura mater was not adherent to the posterior wall of the frontal sinus, which macroscopically showed no sign of disease.

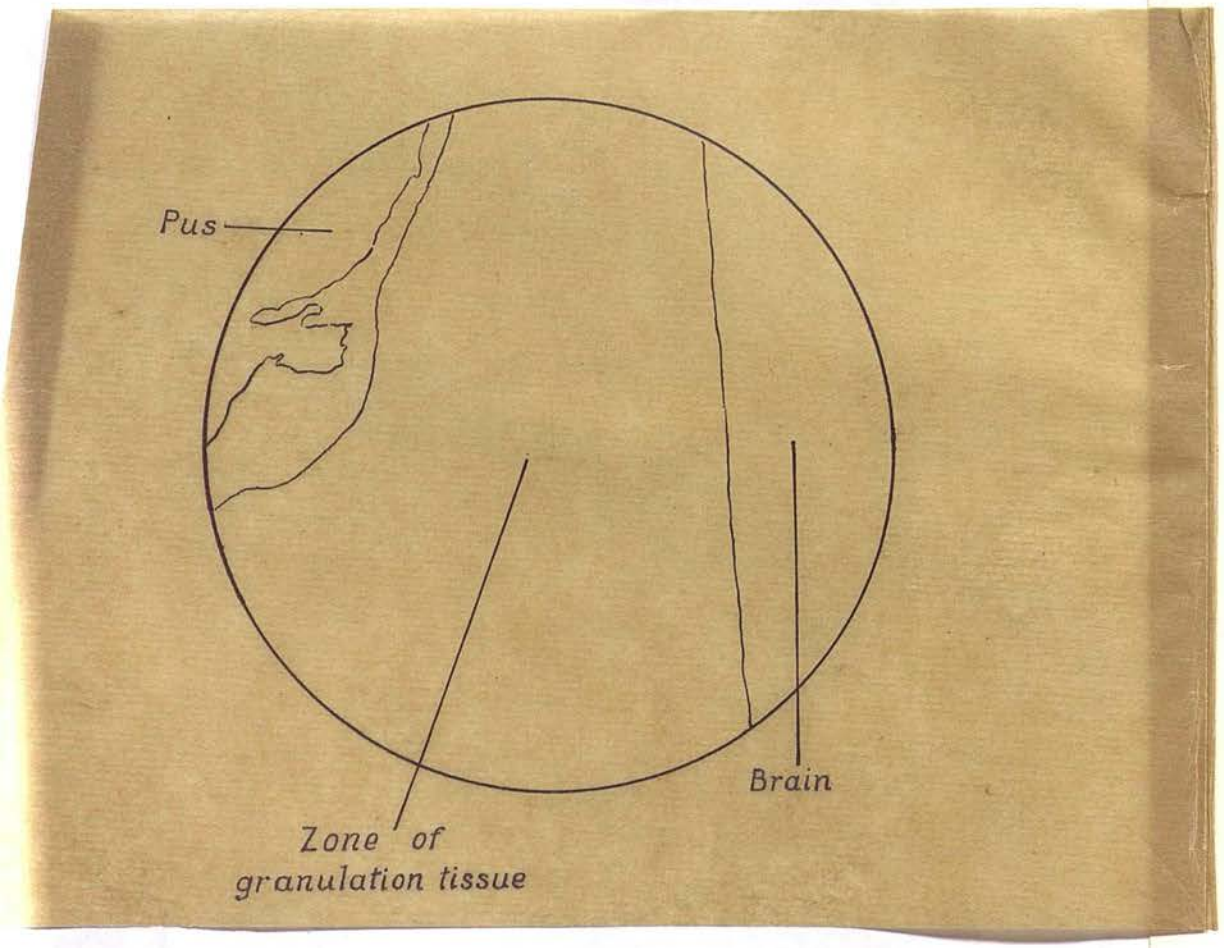
Report on the Material examined Microscopically.

Dr Glass supplied the following portions of

tissue. Two pieces of the cerebral wall of the frontal sinus removed by trephine from the extension lying above the right eye; the mucous membrane of the frontal sinus was attached to these. There was also sent the dura mater adherent to the brain immediately anterior to the abscess. A third specimen comprised the anterior and posterior walls of a portion of the sinus with the lining mucous membrane of the cavity.

Anterior and Posterior Walls of the Frontal Sinus and attached Mucosa.- The lining epithelium was intact, but in places the cells tended to be flattened in type. The mucous membrane was thickened and densely infiltrated by larger and smaller rounded mononucleated cells. The smaller blood vessels were dilated.

Subjacent to the mucous membrane of both the anterior and posterior walls there was a layer of loose fibrous tissue in which a considerable amount of new bone had been formed. This was arranged in spicules and trabeculae. It was more cellular than the old bone and in its formation it was enclosing portions of the loose fibrous tissue matrix along with blood vessels to form Haversian canals. In places, multinucleated giant osteoclasts were present.



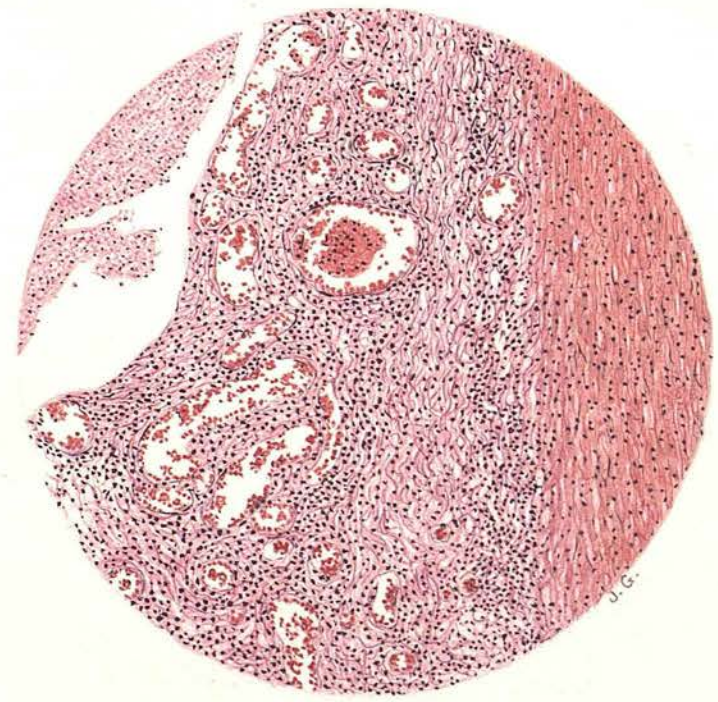


Fig.59.- The section shows the granulation tissue which has formed adhesions between the surface of the brain and the dura mater (pachymeningitis interna).
(Stained by haematin and eosin.)

To face page 231.

In the pre-existing bone, some of the Haversian canals showed osteoporosis, the absorption taking place by means of large multinucleated osteoclasts.

On the pericranial aspect of the anterior wall of the sinus and also on the dural side of the posterior wall a similar formation of new bone in membrane was present, but the layer was thinner; all this osteophytic process was widespread.

The Dura Mater adherent to the Brain immediately anterior to the Frontal Lobe Abscess.- Over the area present in the section where the brain and dura mater were actually adherent, the greater part of the latter structure had disappeared, the periosteal and subjacent layers having been replaced by granulation tissue (pachymeningitis interna). On the granulations which had been in contact with the bony wall of the sinus, pus was present (Fig.59).

The pial vessels in the area under examination were dilated and the leptomeninges were densely infiltrated by mononucleated cells along with a certain number of polymorphonuclear leucocytes. The brain tissue in the neighbourhood of the adherent portion was very cellular and the adventitial spaces round some of the blood vessels were infiltrated by mononucleated cells. No polymorphonuclear leucocytes

were present in the cerebral tissues in the sections.

Commentary.

In this case the primary source of the intracranial infection was the left frontal sinus which had become infected during an attack of influenza some nine weeks before death. The swelling of both eyelids occurring on the left side four weeks before death was undoubtedly due to infection of the bony floor of the frontal sinus. The infection probably caused cario-necrosis and gave rise to an abscess associated with the roof of the orbit and which was evacuated two weeks before death. The abscess was probably subperiosteal and not actually within the orbital tissues (See Case VI, p.104).

When the patient was admitted to the General Hospital, Nottingham, thirty-six hours before death, the infection had extended not only through the floor but also through the posterior bony wall of the frontal sinus and through the adjacent dura mater. Extension had been comparatively slow and adhesions had formed between the dura mater and the neighbouring surface of the brain. Consequently when the infection reached the pia-arachnoid membranes, it was localised and no general leptomeningitis occurred.

The process continued to advance into the substance of the right frontal lobe and gave rise there to a cerebral abscess.

In this case, death was due probably to cerebral oedema around the abscess.

CASE XVIII. Chronic Suppuration in Ethmoidal Air Cells with Nasal Polypi: Operation: Intra-cranial Haemorrhage: Leptomeningitis: Death: Autopsy.

In this case, as a result of operation on the ethmoidal air cells a haemorrhage occurred into the anterior cranial fossa through a large defect in the roof of a right posterior ethmoidal cell, the defect being due to disease of the bone.

C. H., female, aged 55, was admitted on 2nd January 1928 to the Ear and Throat Department, Royal Infirmary, Edinburgh, under the charge of Dr J. S. Fraser, F.R.C.S.E., to whom I am indebted for the following clinical notes.

A condition of left-sided chronic otitis media had been present for many years and this necessitated a radical mastoid operation. The operation was performed on 3rd January 1928.

Examination of the nasal cavities on admission had revealed nasal polypi on both sides. On 17th January, under local anaesthesia they were removed along with the middle conchae; the ethmoidal air cells were then opened with forceps. The nasal

Case XVIII.

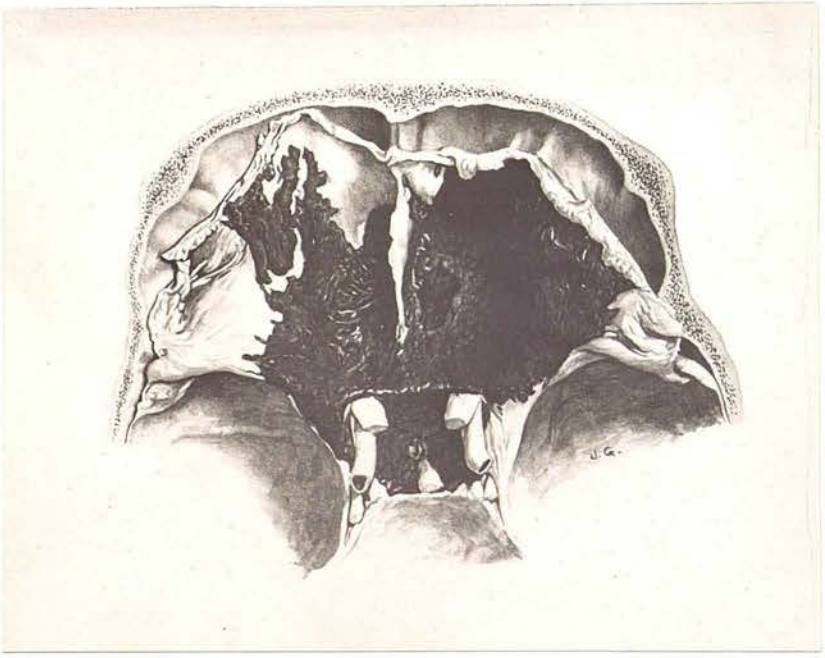


Fig.60.- Photograph of a drawing showing the large haemorrhage into the anterior cranial fossa and the defect, due to disease, in the dura mater and bone lateral and posterior to the cribriform plate on the right side.

To face page 235.

cavities were not plugged.

When the patient blew down the left side of her nose after the operation, air entered the left upper eyelid. A cotton wool pad and bandage were applied and the patient instructed not to blow the nose.

In the evening, considerable haemorrhage occurred from the right side of the nose necessitating the insertion of gauze packing.

On 18th January, in the morning the patient was restless and the temperature was 100°F. The packing was removed from the nose, but owing to profuse haemorrhage the cavity was again plugged. The temperature during the day varied from 104·4°F. to 106°F. The patient became collapsed and semiconscious, but showed no definite signs of leptomeningitis. She died at 1 a.m. on 19th January.

Autopsy.- On reflecting the dura mater, no leptomeningitis was observed. On raising the brain from the cranial floor a thick layer of blood was found to cover the cerebral surface of the dura mater over the greater part of the floor of the anterior cranial fossa (Fig. 60). Anteriorly it reached the plane of the cribriform plate and the anterior margin of both orbital plates. Posteriorly it extended to the prominent margin of the dorsum sellae and posterior

clinoid processes and laterally from here it was limited by the free margin of the lesser wings of the sphenoid bone. The clot was rather more extensive on the right than on the left side.

On further examination, a defect was found in the underlying dura mater and bone lateral and posterior to the cribriform plate on the right side. The aperture measured 12 mm. in its antero-posterior diameter and 8 mm. laterally; it was situated 3 cm. from the inner table of the vertical portion of the frontal bone in front and 12 mm. anterior to the right optic foramen. The defect was in the roof of one of the right posterior ethmoidal air cells and through it the blood clot in the anterior cranial fossa was continuous with that in the cavity below.

Examination of the left medial orbital wall, the side on which emphysema had occurred when the patient blew her nose immediately after operation, showed, on raising the periosteum, a large defect involving the greater part of the wall. Most of the lacrymal bone and the lamina papyracea of the ethmoid had disappeared. The aperture measured 1·5 cm. in the antero-posterior diameter, while vertically it extended from immediately below the fronto-ethmoidal suture to the maxillo-ethmoidal junction. The edges of the

aperture were smooth, and regular in outline and no detached fragments of bone were present. Blood-clot occupied the ethmoidal cells adjacent to the defect, but none was present immediately beneath the orbital periosteum.

Bacteriology.- Microscopical sections of a portion of the blood-clot stained for bacteria showed a moderate number of Gram-positive cocci to be present. Direct films of a swab taken from the leptomeninges demonstrated Gram-positive cocci and a pure growth of a haemolytic streptococcus was obtained on culture media.

Report on the Material removed for Microscopic Examination.

At autopsy a large block of bone was removed from the base of the skull; this included the defect in the roof of the right posterior ethmoidal cell. After decalcifying in Parenny's solution, the block was cut in the coronal plane through the middle of the defect; the tissue was then embedded in paraffin and serial sections made.

1. The mucous membrane of the ethmoidal cell, the roof of which contained the aperture, was densely infiltrated by polymorphonuclear leucocytes, large and small rounded mononucleated cells, and red blood

corpuscles. The bone forming the margins of the aperture was necrosed; its Haversian canals were enlarged, their structural elements had disappeared, and they contained pus. The fibrous dura mater was continuous around the bony margin with the remains of the mucous membrane lining the ethmoidal cell.

Elsewhere the bone showed chronic inflammatory changes, varying only in degree from those described above.

The condition in the bone, therefore, was one of chronic purulent inflammation with cario-necrosis and the aperture had been formed in the progressive course of the process.

2. Sections of the leptomeninges showed acute purulent inflammation; the pial blood vessels were greatly dilated and a large amount of cellular exudate was present in the pia-arachnoid meshes. The cells of the exudate were for the most part polymorphonuclear leucocytes and large rounded mononucleated cells.

Commentary.

In this case, bilateral chronic suppuration in the ethmoidal air cells had existed for some time. The bone of the ethmoidal labyrinth on both sides had become affected and cario-necrosis had resulted in a

large perforation of the laminae papyracea and lacrymal bone on the left side. On the right side a similar process had produced a large aperture in the roof of one of the posterior ethmoidal cells and in the overlying dura mater. After operation on the ethmoidal labyrinths, the patient blew down the left side of the nose and air was forced into the tissues of the left orbit. This accident gave rise to no untoward result.

Some hours after the operation, however, the patient began to bleed from the right side of the nose and this necessitated packing. As revealed at autopsy, the haemorrhage had continued, the blood passing through the defect in the roof of the ethmoid labyrinth into the anterior cranial fossa. Infection of the leptomeninges occurred and the patient died some thirty-six hours after the operation.

Death in this instance was due to a combination of several factors. The haemorrhage into the leptomeninges was considerable in amount and this of itself would cause an appreciable increase of pressure on the brain. Again, although acute leptomeningitis could not be recognised either before death or on inspection at the autopsy, not only were bacteria demonstrated in direct films made from a swab of the leptomeninges

and a growth of haemolytic streptococci obtained on culture media, but also microscopical sections showed a copious purulent exudate to be present. Lastly, it is a well recognised fact that the onset of a haemorrhage into the cerebral substance or any other sudden injury which involves the cerebral cortex is usually marked by profound shock and loss of consciousness. It is reasonable to suppose that a haemorrhage of the size and extent of that which occurred into the leptomeninges in the present case, would have an effect on the cerebral equilibrium of a similar nature even though less in degree. This suggestion is supported by the clinical observation that some twelve hours before she died, the patient became collapsed and semiconscious.

CASE XIX. Chronic Suppuration of Left Frontal Air Sinus: Radical Operation on the Sinus: Acute Leptomeningitis: Early Abscess in Left Frontal Lobe: Death: Autopsy.

J.R., female, aged 80, was transferred from the Eye Department to the Ear and Throat Department, Royal Infirmary, Edinburgh, on 1st February, 1924, for examination of the nasal cavities and nasal accessory sinuses. I am indebted to Dr J. S. Fraser, F.R.C.S.E., for the following clinical notes.

A swelling of almost bony hardness was present in the left orbit in the position of the floor of the frontal sinus, and pus could be expressed from a small opening on the surface. A polypus and pus were visible in the left nasal cavity and pus was seen on the posterior surface of the soft palate. X-ray examination revealed a large, shadowed left frontal sinus and a cloudy appearance of the left antrum.

On 5th February, the left frontal sinus was exposed. The cavity contained foul smelling pus and a large aperture was present in the floor; the bone surrounding the aperture was soft. The posterior wall of the cavity was eroded in two situations.

The anterior wall of the sinus was removed along with what remained of the bony floor and the whole of the mucous membrane. A large opening was made into the nose, the middle concha and ethmoidal cells being removed. A light iodoform gauze packing was introduced and a large drainage opening was left in the centre of the skin incision.

On 6th February, the patient vomited frequently; the temperature was 99.6° F. and the pulse rate 96.

On 8th February, when the wound was dressed it looked satisfactory. The temperature had continued somewhat raised, it being about 99° F.

On 9th February, in the evening, the patient became unconscious and died at 2-30 a.m. on 10th February, four and a half days after the operation.

Autopsy.- An excess of cerebrospinal fluid was present; it was turbid and greenish in colour. Purulent leptomeningitis was found over the frontal lobes, vertex and base of the brain. Immediately opposite the apertures in the posterior bony wall of the frontal sinus a small red area of softening was present just below the surface of the left frontal lobe.

The lungs showed commencing hypostatic pneumonia at their bases. The changes presented by the

internal organs were compatible with the age of the patient.

Report on the Material examined Microscopically.

1. The Leptomeninges and Brain.- The pia-arachnoid spaces were densely infiltrated by polymorphonuclear leucocytes and large rounded mononucleated cells. The exudate was continuous along the perivascular spaces of the blood vessels, penetrating the substance of the brain.

The small area of red softening found at autopsy immediately below the surface in the anterior portion of the left frontal lobe was an abscess. The cerebral tissue was disintegrated and densely infiltrated by polymorphonuclear leucocytes. Liquefaction was commencing and a few small haemorrhages had occurred into the disintegrated material. The abscess was not sharply demarcated from the surrounding tissue, the polymorphonuclear leucocytes having infiltrated diffusely into it.

The perivascular spaces in the neighbourhood of the abscess were dilated by polymorphonuclear leucocytes and by rounded cells ("granular cells") in various stages of disintegration. In most instances the cytoplasm of the latter cells had completely disappeared, leaving a small round densely staining

nucleus. The perivascular sheaths of many of the larger blood vessels were surrounded by a narrow zone in which the cerebral tissue was undergoing necrobiotic changes.

Serial sections did not demonstrate thrombosed blood vessels, but they showed a track of pus between the abscess and the surface of the brain. The histological picture of the track and its walls was the same as that of the abscess and the cerebral tissue surrounding it. No granulation tissue or adhesions were present in the pia-arachnoid membrane where the track came to the surface. A moderately large pial artery was situated near the superficial end of the track and perforating arteries of considerable size and probably branches of this pial artery were in relation to the wall of the track and in a direction transversely to it. The perivascular sheaths of the perforating arteries were infected.

2. The Cribriform and Olfactory Regions.- Sections made in the coronal plane through the cribriform plate and olfactory regions of the nasal cavities showed that no descending infection of the olfactory perineural sheaths had occurred.

Commentary.

In this case, the patient suffered from chronic suppuration of the left frontal air sinus. This had given rise to cario-necrosis of the bony wall; there was a large aperture in the floor and two defects in the posterior wall. Following operation upon the sinus, the patient developed acute purulent leptomeningitis and death occurred four and a half days after the operation. A small cerebral abscess was present immediately below the surface of the portion of the left frontal lobe in relation to the posterior wall of the diseased air cavity.

Macroscopically the dura mater was not perforated, and none of it was kept for microscopical examination. The process by which the infection passed from the bone to the leptomeninges could not be investigated, therefore, and it must remain a matter of conjecture. Probably infection reached the intradural structures by infiltrating through the layers of the dura mater.

A chronic infective condition may be chronic from the outset, or may result from acute infection passing into a chronic phase. In either event, in the chronic form a partial equilibrium exists between the infection and the antagonizing body factors,

but the infecting agent is always preponderating and hence the disease is slowly progressing. It is easy, therefore, to accept the postulate that the results of the trauma inseparable from an operation must upset the balance between the infecting agent and the tissues. Consequently, the infection hitherto slowly progressing may become more active and rapid in its spread; the present case is an example of this. Moreover, when infection, formerly restrained, reaches other parts, it may become fulminating in type. Thus it occurs that when, as a result of an old-standing and slowly progressive lesion, pyogenic micro-organisms reach the leptomeninges, an acute generalised and rapidly fatal purulent leptomeningitis is produced.

It is necessary to consider the relationship of the small cerebral abscess present in this case to the leptomeningitis, namely, whether the abscess was the direct cause of the acute purulent infection of the meninges or not.

From the histology, it is obvious that the abscess was very acute and recent in its formation. In cases in which acute leptomeningitis arises secondary to a cerebral abscess, the abscess is usually chronic in type. Further, in the present

instance, there is histological evidence though not absolute proof that the infection of the cerebral tissues arose as a result of infection of a perivascular space. The pus in the leptomeninges in this area had penetrated for a considerable distance along the perivascular spaces; the picture obtained from the series of microscopical preparations certainly suggests that the short track between the abscess and the surface had been formed along a vascular prolongation of the pia mater into the brain, and that the infection had penetrated from this into the cerebral substance. The portion which has been designated the abscess is merely the further development of the same process. In the writer's opinion, therefore, there is no doubt that, in this instance, the acute leptomeningitis arose by spread of infection from the diseased air sinus and that the small abscess was merely an expression of the same process.

Finally, for the sake of completeness, it should be stated that the mononucleated cells in various stages of disintegration (the so-called "granule cells") in the perivascular sheaths are seen in all lesions of the central nervous system involving destruction of its substance; their function is to

help in the removal of the disintegrating parenchymal and interstitial tissue. To discuss this question further, however, would be outside the province of the present Thesis.

VI. INFECTION OF THE INTRACRANIAL STRUCTURES BY THE OLFACTORY PERINEURAL SHEATHS.

VI. INFECTION OF THE INTRACRANIAL STRUCTURES BY THE OLFACTORY PERINEURAL SHEATHS.

In the Introduction, mention has been made (pg.2) of the lymph system which begins in the dura mater and drains through the jugular and other foramina into the deep cervical lymph nodes. This system has no direct openings into the pia-arachnoid spaces.

Moreover, from both an anatomical and a pathological standpoint, the dura mater must be considered a part of the "cranium" and not an intracranial structure. The osseous layer of the dura mater forms a periosteum to the bone, and the areolar tissue of the Haversian canals is continuous with its fibrous elements. This portion of the dura mater, therefore, has exactly the same anatomical and physiological relationship to the bone as has the external periosteum. The inner layers of the dura mater are essentially of the same general structure as are the layers adjacent to the bone, the only difference being one of degree; the fibrous laminae forming the periosteal layers are dense, whereas the inner ones are rather more loosely arranged.

From the nature of its elements, the dura mater offers resistance to the passage of infection and of other pathological processes as great if not greater than the bone itself. This is easily understood since, firstly, the red marrow of the cranial bones is a particularly favourable nidus for the development of infection reaching it from peripheral foci of inflammation, and secondly, free vascular communication exists between its blood spaces and the dural blood sinuses. No analagous structure to the bone marrow exists in the dura mater; although the membrane serves for the transmission of blood vessels and although it is used to form the walls of the blood sinuses, the dura mater proper, as other fibrous membranes, is a structure of relatively little vascularity.

It has been stated (pg.3) that apart from the optic sheath, the only peripheral structures in the anterior part of the skull which are in direct communication with the pia-arachnoid spaces are the perineural sheaths of the olfactory nerves. It is necessary at this point to consider in greater detail the lymphatic system of the nasal mucous membrane and its relation to the olfactory perineural sheaths.

The Lymphatics of the Nasal Mucous Membrane.

The subepithelial capillary lymphatic network of the nasal mucous membrane varies in the richness of its development in different areas. The vessels are more numerous on the inferior and middle turbinal and in the region of the choana; on the septum and superior turbinal and in the mucosa immediately posterior to the nasal vestibule they are less abundant. Key and Retzius have stated that some of the mucosal lymphatics open upon the epithelial surface, but there seems no doubt that this conclusion was based upon the appearances produced by the use of excessive pressure in the injection experiments employed (Cunéo and André). As elsewhere in the body, the lymphatic system is closed on the free epithelial surface.

It is customary to describe the nasal lymphatics according to their arrangement in the respiratory and olfactory regions of the nasal cavity, although the vessels in the two areas are not entirely independent.

Respiratory Area.- The respiratory area comprises that portion of the nasal cavity which is bounded laterally by the middle and inferior turbinals. The general direction of the flow of lymph in

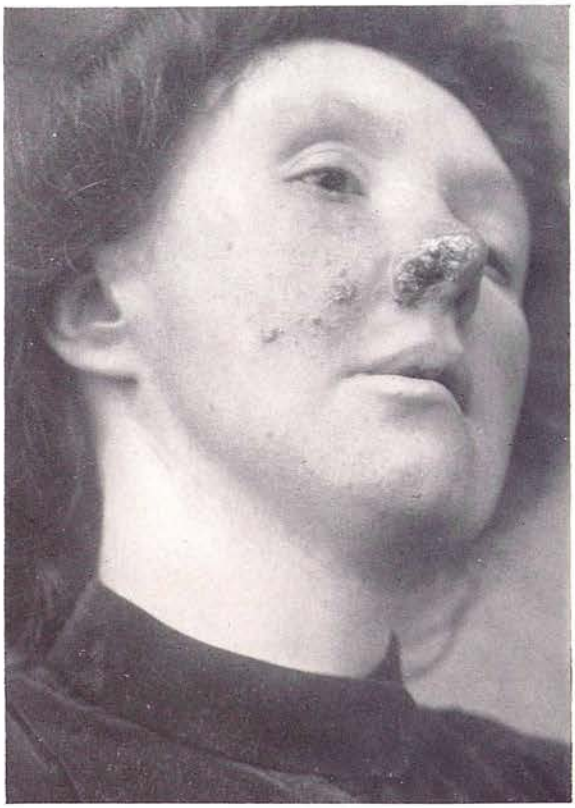


Fig.60a.- From a photograph kindly lent to the author by Dr A. Logan Turner. Lupus of the nasal mucosa just posterior to the vestibule with secondary cutaneous infection. The condition illustrates the connection between the lymphatics of the nasal mucosa and those of the skin.

To face page 253.

this area is in an antero-posterior direction. In the most anterior part of the nasal mucosa the collecting trunks pass forwards and join the cutaneous lymphatics of the nasal vestibule, the external nose and the cheek. Accompanying the external maxillary vein (facial vein) the lymphatics reach the submaxillary lymph nodes, whose efferents in turn terminate in the superior deep cervical nodes.

The connection between the lymphatics of the anterior part of the nasal mucosa and those of the skin is illustrated in Fig.60a, reproduced from the photograph of a patient affected with lupus of the nasal mucosa immediately within the vestibule. The disease, spreading along the lymphatic vessels, invaded the ala nasi and extended thence across the cheek, indicating its passage by the formation of small cutaneous nodules of lupus. Beneath the mandible, a long scar marked the position of a surgical operation for the removal of the infected superior deep cervical lymph nodes.

The main lymphatic stream in the respiratory area of the nasal cavities, however, is directed backwards in collecting trunks which pass through the posterior naris into the pharynx. Some of these vessels course laterally and downwards along with the

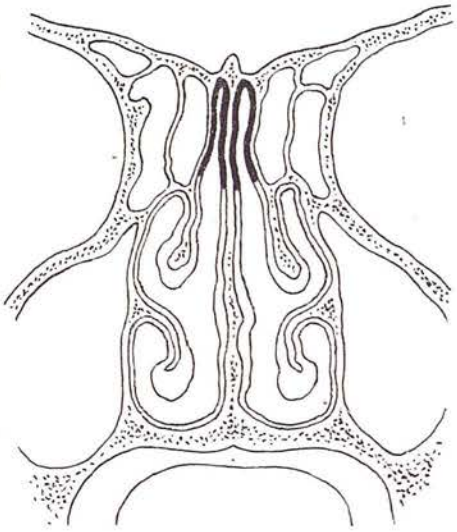


Fig.60b.- The broad black lines represent the distribution of the olfactory nerve filaments on the nasal septum and superior turbinals.

To face page 254

lymphatics of the soft palate and tonsillar region and pass with the pharyngeal lymphatics into the superior deep cervical nodes. Other collecting trunks, and probably the most important of those draining the nasal mucosa, enter the lateral retropharyngeal lymph nodes whose efferents open also into the superior deep cervical nodes.

The Olfactory Area.- The filaments of the olfactory nerve, about twenty in number, are situated in the nasal mucous membrane over an area occupying the upper third of the nasal septum and nearly the whole of the opposed superior concha. Their septal distribution is somewhat more extensive than that on the lateral nasal wall (Fig.60b).

From this area the collecting lymphatic trunks are directed backwards to the choana; those from the lateral wall link up with the lymph vessels of the lateral nasopharyngeal wall in the region of the Eustachian tube, while those on the septum, coursing along the superior surface of the soft palate, in conjunction with similar trunks from the respiratory area, also join the pharyngeal lymphatics. Hence all the lymph from the mucous membrane of the interior of the nose, whether conveyed forwards or backwards, finally reaches the superior deep cervical

nodes.

The Olfactory Perineural Sheaths and their Relation to the Pia-arachnoid Spaces.- The researches of Key, Retzius, Schwalbe, and other anatomists have demonstrated the presence of perineural spaces surrounding the olfactory nerves. They have also shown that by injecting the pia-arachnoid spaces in animals, it was possible to fill the perineural spaces in the olfactory mucosa. Cunéo, André and Zwillinger obtained the same results in experiments upon young human subjects; further, they observed that the injection material also passed into the superficial lymphatic network of the olfactory mucous membrane. From these experiments they concluded that they had established continuity not only between the meningeal spaces and the spaces within the olfactory nerve sheaths, but also with the lymphatic network of the olfactory nasal mucosa. On developmental and anatomical grounds, however, it seems more probable that the injection did not enter the mucosal lymphatic network directly through foramina in the cribriform plate, but that it percolated from within the perineural sheaths through the tissue spaces into the lymphatic vessels of the mucous membrane.

As already stated, the central nervous system

does not possess lymphatic vessels in the ordinary meaning of the term, the meningeal spaces being quite independent of the lymphatic system. In all probability, therefore, there is no direct communication between the sub-arachnoid space and the lymphatics of the nasal mucosa. On the other hand, the perineural sheaths effect a communication with the pia-arachnoid spaces, a fact which has been demonstrated not only by experiment but also pathologically, as shown by the microscope in the following four cases.

CASE XX. Nasal Mucous Polypi: Intranasal Operation on the Ethmoidal Air Cells: Purulent Leptomeningitis: Death: Autopsy.

J. B., male, aged 33, was admitted to the Royal Infirmary, Edinburgh, on 21st August 1923, under the care of Dr G. Ewart Martin, F.R.C.S.E., to whom I am indebted for the clinical notes of the case. The patient complained of chronic nasal obstruction and postnasal discharge; otherwise he enjoyed good health.

Examination showed a large polypus in the left nasal cavity, attached to the anterior end of the middle concha; several smaller polypi were seen posterior to it. Pus was present in the left choana. Polypi were also present in the right nasal cavity. The skiagram suggested normal frontal sinuses and the ethmoidal areas were fairly well defined; the right antrum was duller than that on the left side.

22nd August.- Both ethmoidal labyrinths were operated upon by Sluder's method and thus, on each side, the superior and middle conchae were removed and the ethmoidal air cells opened. The bony walls of the ethmoidal cells were soft and friable; the sphenoidal sinuses were not interfered with. No

nasal tampons were inserted after the operation.

23rd August.- During the afternoon of the day following the operation, the temperature, previously normal, rose to 103·8°F.; severe headache was complained of and the patient became delirious in the evening.

24th August.- The cerebrospinal fluid obtained by lumbar puncture was turbid and later gave a pure growth of Pneumococci.

26th August.- The patient became unconscious and died in the evening, on the fourth day after the operation.

Autopsy.- This was limited to the head and revealed diffuse purulent basal leptomeningitis. No naked-eye change was present in the bony walls of the air sinuses on their cranial aspect. The frontal and maxillary cavities were healthy. A pure culture of Pneumococcus was obtained from the pus in the leptomeninges covering the base of the brain. A large block, containing the ethmoidal and sphenoidal sinuses was preserved for microscopic examination. After decalcification the material was subdivided in the coronal plane into pieces suitable for embedding in paraffin. From each block serial sections were made in the coronal plane from before backwards.

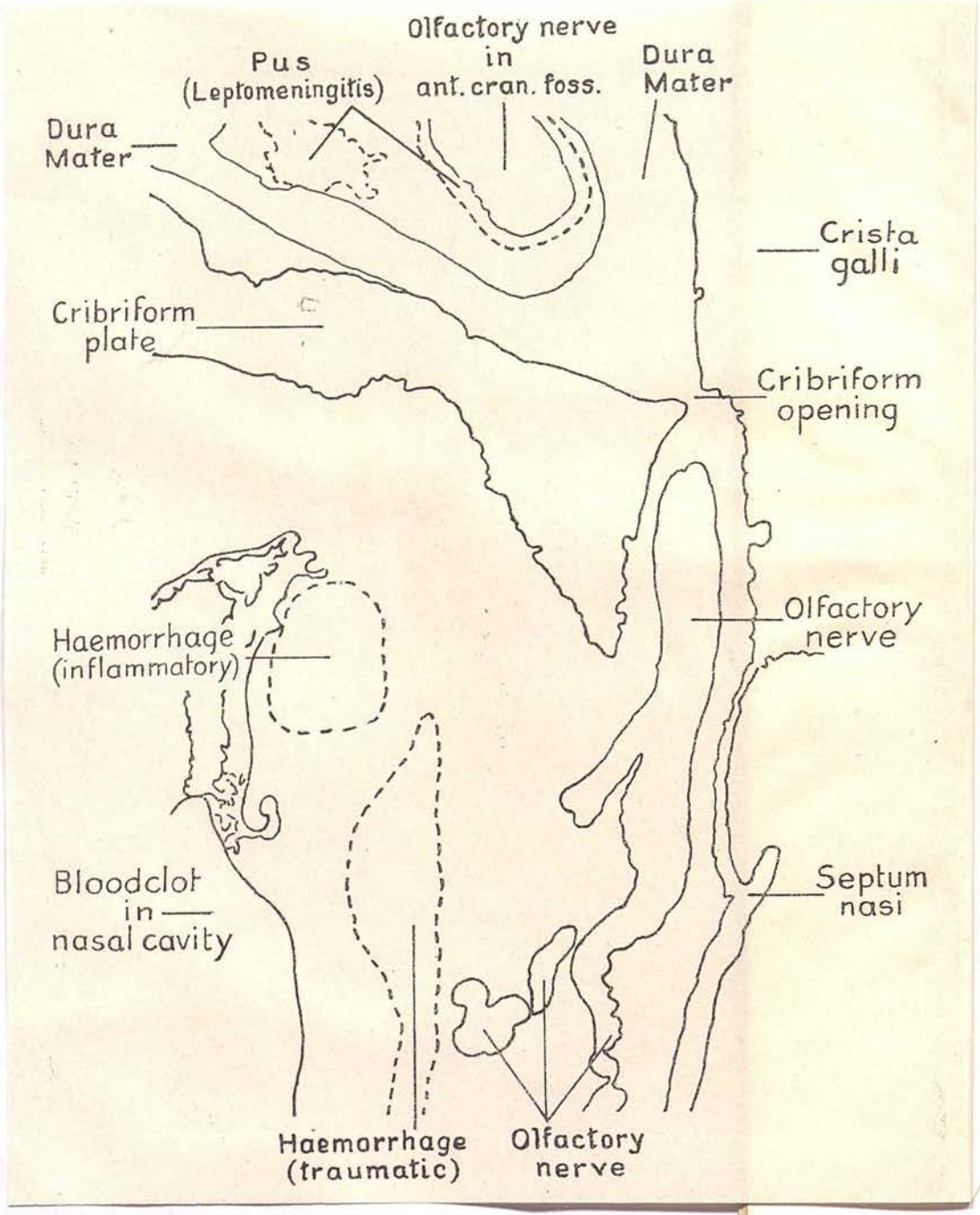


Fig.61.- Coronal section through olfactory region of the right nasal cavity, showing inflamed mucous membrane and an olfactory nerve with purulent infiltration of its sheath. (Stained by haematoxylin and eosin.)

To face page 259.

Report on the Material examined Microscopically.

On the right side a considerable portion of the naso-ethmoidal bony wall and its covering of mucous membrane had been removed by the surgical operation. The superficial layers of the mucosa of the naso-ethmoidal cavity thus formed, and of the adjacent part of the nasal septum, had been torn away from the deeper layers. The deeper layers, on the other hand, varying in thickness in different areas, remained in situ. A considerable quantity of blood-clot was present in the right nasal cavity and contiguous ethmoidal cell.

On the left side none of the olfactory mucous membrane had been removed, but there were haemorrhages, resulting from trauma, in its layers. The upper part of the bony wall between the olfactory portion of the nasal cavity and the left ethmoidal cells was complete.

1. The Changes in the Olfactory Mucous Membrane of the Nasal Cavities.- The mucous membrane of the olfactory area on both sides of the nose showed its normal lining of non-ciliated columnar epithelium; in certain areas the lining cells had become flattened in type. The superficial layers of the mucosa were densely infiltrated by small and large, round,

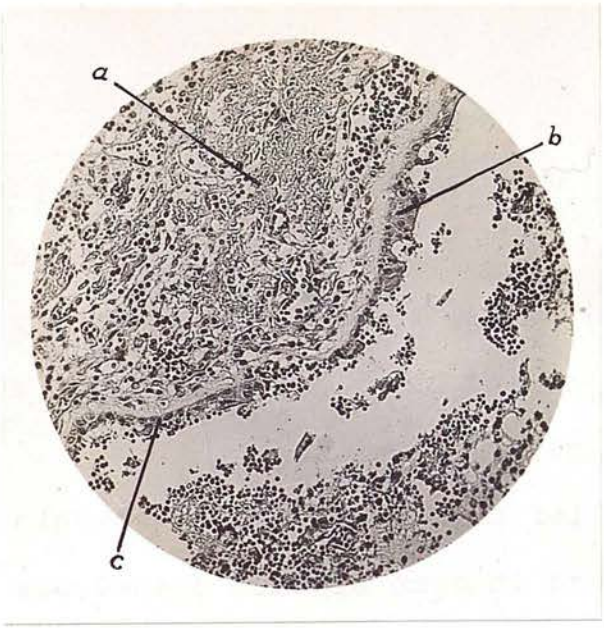


Fig.62.- Right olfactory nasal mucosa (a) showing an area of columnar (b) and of flattened (c) lining epithelium; the subepithelial tissue shows dilated blood vessels and infiltration by mononucleated and a few polymorphonuclear cells.

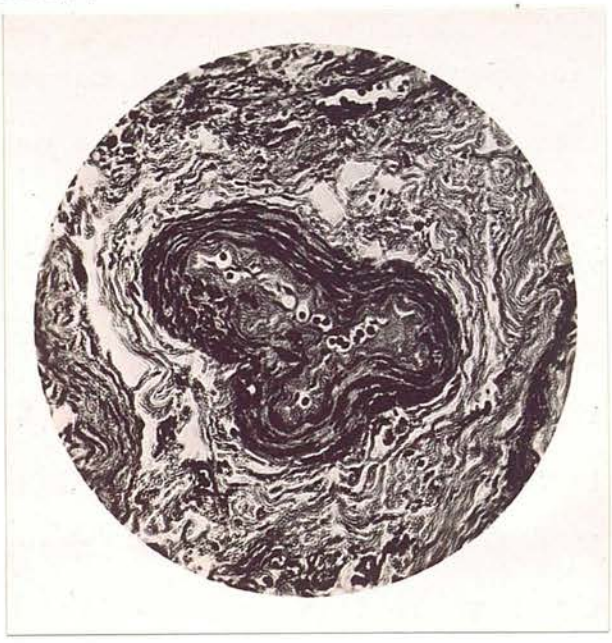


Fig.63.- Artery in the deep layer of the right nasal mucosa; its wall is greatly thickened by fibrous tissue.

To face page 260.

mononucleated cells and by a few polymorphonuclears (Fig.62). Many of the arteries in the deeper mucosa had thickened walls, the thickening mainly involving the middle coat and being largely of a fibrous character (Fig.62).

The smaller thin-walled blood-vessels were greatly dilated, and in some of them diapedesis of polymorphonuclear leucocytes was active. The mucosa was thickened and oedematous; haemorrhages, some of them due to trauma, were seen. No thrombosed veins were present.

The bony roof of both nasal cavities showed some osteoclastic destruction beneath the mucosa; this process was also present in some of the contiguous Haversian spaces.

The above changes demonstrate, therefore, an acute infection superimposed on a chronic inflammation.

2. Olfactory Nerves in the Mucosa of the Nasal Septum and Lateral Wall of the Nasal Cavities.- On both sides the olfactory nerves were traced upwards through the cribriform openings and through the dura mater into the cranial cavity.

(a) In the right nasal cavity the perineural sheaths of the branches of the olfactory nerves lying in the septal mucosa were dilated and invaded by

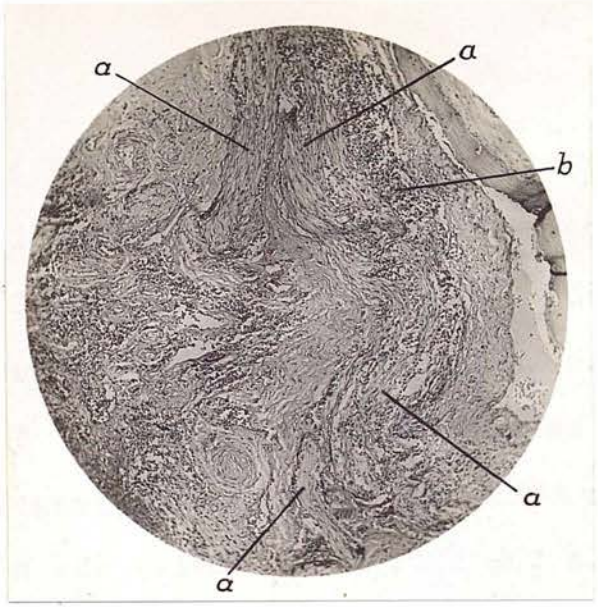


Fig.64.- A right olfactory nerve (a) in the mucosa of the nasal septum; the perineural sheath (b) contains numerous polymorphonuclear leucocytes.

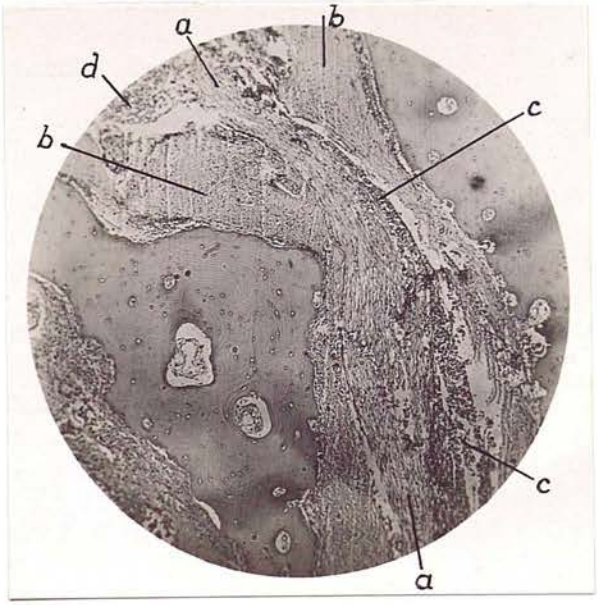


Fig.65.- The same nerve (a) as in Fig.64, passing through the cribriform opening and dura mater (b). The pus in the perineural sheath (c) is continuous with that in the pia-arachnoid meshes (d).

To face page 261.

numerous polymorphonuclear leucocytes (Figs.61 and 64). The pus was continuous with that in the pia-arachnoid spaces (Fig.65). Here and there in the larger nerve trunks the pus had ruptured the perineurium and was infiltrating between the nerve fibres. The fibres themselves on this side were more or less intact.

(b) In the left nasal cavity the nerve fibres had disappeared and the canals thus formed were full of pus (Fig.66). Higher up the pus was continuous with that in the pia-arachnoid spaces.

3. The Ethmoidal Cells - (a) The Right Ethmoidal Cells.- The deep layers of the mucosa which had not been removed at the operation showed numerous petechial haemorrhages. The smaller blood vessels were dilated and active diapedesis of polymorphonuclear leucocytes was occurring through their walls. The tissue was infiltrated by small and large, round and elongated mononucleated cells and polymorphonuclear leucocytes.

Lateral to the cribriform plate a traumatic fracture of the roof of one of the right ethmoidal cells was present, the bone being absent over a small area (Fig.67). The fracture had been produced at the edge of a Haversian opening in the osseous plate; through the hiatus thus formed, a small quantity of

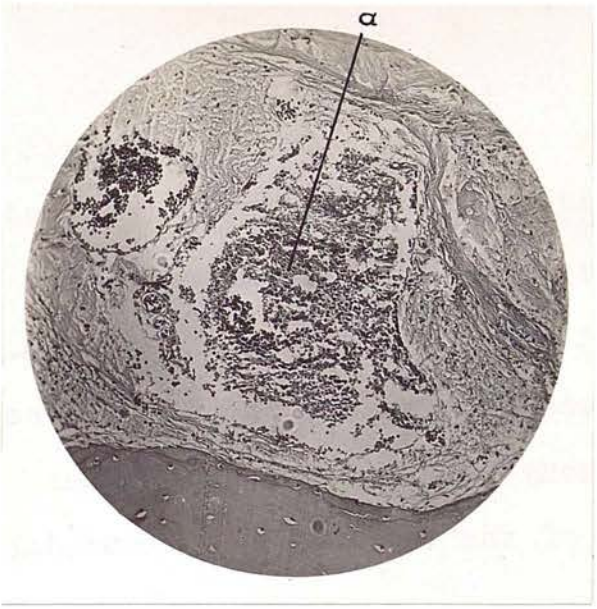


Fig.66.- Tract of a left olfactory nerve in the dura mater. The nerve fibres have disappeared and the canal is full of pus (a).

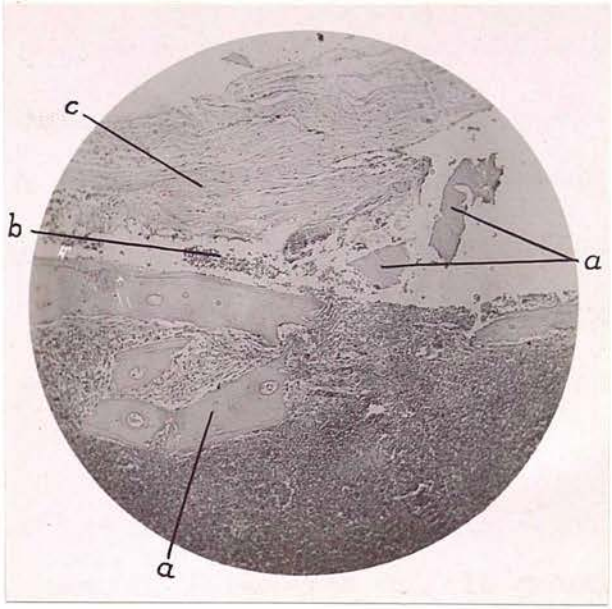


Fig.67.- Traumatic fracture in the roof of a right ethmoidal cell. No infection is present in the neighbourhood.

(a) Fragments of bone.
(b) Extravasated blood.
(c) Dura mater.

To face page 262.

the blood, extravasated into the air-cell at the operation, had passed between the bone and the periosteal layer of the dura mater. The bone which was fractured was extremely thin, and minute fragments were seen both within the ethmoid cell and between the bony roof and the dura mater. At the lateral edge of the fracture the ethmoidal periostium retained its continuity with the periosteum covering the fragments of bone lying in the blood clot in the air cavity. The tissue cells in the deeper layer of the ethmoidal mucosa in the immediate neighbourhood of the fracture were slightly swollen, but no polymorphonuclear leucocytes were present.

The tissue cells were therefore reacting; the reaction was due probably in part to the fracture and in part to the presence of the blood-clot, both resulting from the trauma. No infection, however, was present in its immediate vicinity, nor had passed to the meninges by way of the fracture.

(b) The Left Ethmoidal Air-Cells.- On this side the lining mucosa of the air-cells showed early acute inflammatory changes. Many of the smaller veins were greatly dilated, but polymorphonuclear diapedesis, although present, was not a prominent feature. The superficial layers of the mucous membrane were

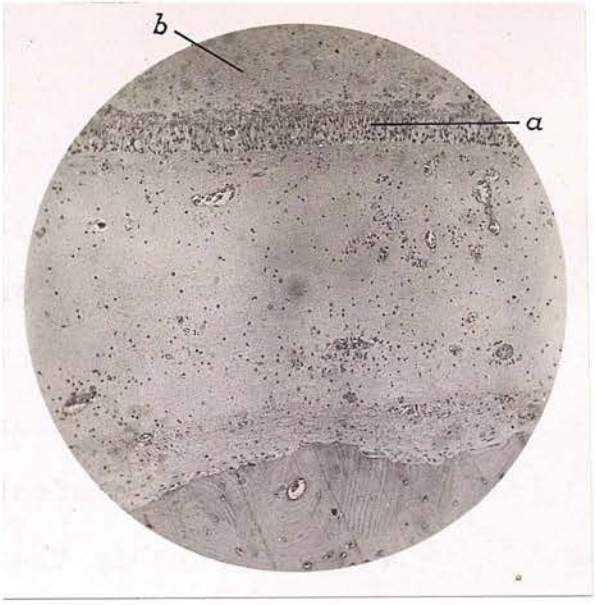


Fig.68.- Left sphenoidal air sinus. The mucosa, lined by columnar epithelium (a) shows early inflammatory change; the cavity contains muco-pus (b).

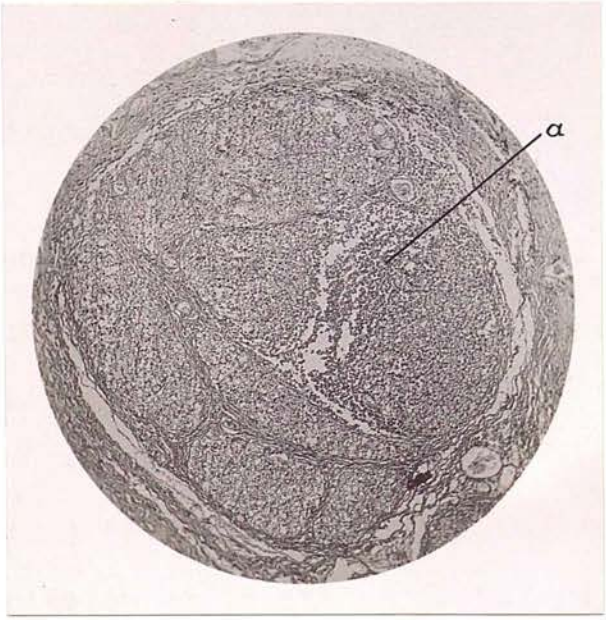


Fig.69.- One of the bundles of the ophthalmic division of the left 5th cranial nerve in the lateral wall of the cavernous blood sinus. Pus (a) has penetrated the perineurium and lies between the nerve fibres.

To face page 263.

infiltrated by large and small mononucleated cells, together with a few plasma cells; throughout the mucous membrane, petechial haemorrhages were present.

On both sides the character of the cells infiltrating the superficial part of the mucous membrane indicated the presence of a chronic infective process; the early acute changes were probably the result of infection and not merely consequent upon trauma.

4. The Sphenoidal Air Sinuses (Fig.68).- The right sinus contained a considerable quantity of mucous secretion, but no pus. In the left cavity, on the other hand, there was a large amount of mucus containing many polymorphonuclear cells.

In both air-sinuses the columnar epithelium was intact and the mucosa of each showed the same changes, but these were more pronounced on the left side. They consisted in oedematous thickening with areas of infiltration by large and small round cells with scattered polymorphonuclear leucocytes. Active diapedesis of leucocytes had occurred in relation to many of the smaller blood-vessels, especially in the deeper layer of the mucosa. Occasional small petechial haemorrhages were seen in the mucous membrane.

The bone beneath the mucous lining of the right

sinus showed no osteoporotic changes. In some of the sections from the left sinus, however, very slight and early activity on the part of the osteoclasts was seen in the bone underlying the mucous membrane. The red marrow of the sinus wall showed no infection.

In both sphenoidal sinuses, therefore, the changes observed were those of early acute inflammation.

5. The Cavernous Blood Sinuses.- The cavernous spaces on both sides contained non-infected post-mortem blood-clot.

6. The Leptomeninges.- The areolar tissue surrounding the nerve bundles in the lateral walls of both cavernous sinuses was densely infiltrated by pus, this being part of the general purulent leptomeningitis. In one of the trunks of the ophthalmic division of the left fifth cranial nerve, the pus had penetrated through the nerve sheath and was lying between the individual nerve fibres (Fig.69).

The Pathway of Infection in this Case.- Microscopic examination has demonstrated a chronic inflammation of the nasal mucosa, a superimposed acute infection and the olfactory perineural sheaths infiltrated by pus.

Infection of the leptomeninges was not secondary

to thrombosis of the cavernous blood sinus, as this structure and its tributaries contained no septic clot.

Further, infection by direct extension through the bone has been shown to be absent.

Hence infection of the leptomeninges took place by the olfactory perineural sheaths.

During operation on the olfactory mucous membrane, the perineural sheaths of the olfactory nerves are necessarily opened up; at the same time, should a chronic infection of the mucosa be present, there is always the risk of converting it into an acute inflammation. Hence the acute infection has ready access to the perineural spaces and thence to the meninges.

To summarise the present case: An acute inflammation of the nasal mucous membrane was superimposed on a chronic infection. On both sides the infection passed up the olfactory perineural tracts and spread directly into the pia-arachnoid spaces around the intra-dural portions of the olfactory nerves. On the left side the nerve fibres had degenerated and disappeared completely, the pus filling the whole neural tract. On the right side the changes were not so advanced, the nerve fibres being still present.

Fig.70.- M.W. Otitic leptomeningitis. Section shows a left olfactory nerve (a) passing through the dura mater (b) into a cribriform opening; the perineural sheath (c) is infiltrated by pus.

Fig.71.- M.W. Otitic leptomeningitis. Section shows a right olfactory nerve (a) in the nasal mucosa immediately below a cribriform opening; the perineural sheath is slightly infiltrated by inflammatory cells.

To face page 266.

Ascending and Descending Infection of the Olfactory Perineural Sheaths.- The writer had the opportunity of examining microscopically the olfactory nasal mucous membrane of a girl, M.W., aged 13., who died as a result of generalised purulent leptomeningitis secondary to chronic suppuration in the left middle ear. Like J.B. Case XX, she also died on the fifth day of the illness.

In both cases microscopic examination demonstrated an acute inflammatory infiltration of the olfactory perineural sheaths, and in both the pus within the sheaths was continuous with that in the pia-arachnoid spaces.

In the two cases, however, certain differences may be observed both in the amount of pus within the nerve sheaths and in the extent of its distribution. Thus, in the case of leptomeningitis of otitic origin, the perineural spaces are not so widely dilated; the pus which is smaller in amount is present only round the larger nerve branches and in the vicinity of the cribriform openings (Figs. 70 and 71); it is not distributed within the perineural sheaths of the smaller olfactory branches in the nasal mucosa. Further, in no situation have the nerve fibres been destroyed by the pus. These histological changes were similar in

both nasal cavities. When these facts are studied in connection with the clinical features of the case, they point to a descending infection of the perineural sheaths during the terminal stage of the generalised leptomeningitis.

On the other hand, in Case XX, the cellular infiltration of the perineural sheaths was considerable in amount and could be traced along the nerve branches in the olfactory nasal mucosa. The changes were also more advanced; on the right side the pus had ruptured the perineurium in more than one situation and was infiltrating between the nerve fibres, while on the left side the fibres had disappeared, the canals thus formed being filled with pus. Hence, the changes suggest an inflammatory process of considerably longer duration than in the other case, although the period of the illness was the same in both; when taken in conjunction with the clinical history, they undoubtedly support an ascending infection of the olfactory perineural sheaths, which began early in the course of the illness.

CASE XXI. Nasal Mucous Polypi: Intranasal Operation on the Ethmoidal Air Cells: Purulent Leptomeningitis: Death: Autopsy.

The present case is another example of acute purulent leptomeningitis, supervening upon operation on the ethmoidal air cavities, and like the preceding Case XX., the microscopic examination of the tissues demonstrates that the infection spread along the perineural sheaths of the olfactory nerves.

M.M., spinster, aged 66, a weaver by occupation, was admitted to the Ear and Throat Department, Royal Infirmary, Edinburgh, on 6th October 1925, under the care of Mr J. D. Lithgow, F.R.C.S.E., to whom I am indebted for the following clinical notes.

The patient had complained of bilateral nasal obstruction for a period of five months. This was associated with slight nasal discharge and with dull headache in the frontal region. The hearing in both ears was somewhat impaired.

Examination showed that the nasal septum was deflected to the left. Both middle conchae were oedematous. X-ray films revealed a shadowed right antrum; the ethmoidal air cells were not clearly defined; the frontal sinuses were not delineated.

On 7th October, under local anaesthesia, both ethmoidal labyrinths were operated upon by Sluder's method, the superior and middle conchae being removed on each side and the ethmoidal air cells opened up. The sphenoidal sinuses were not interfered with.

On 8th October the patient complained of headache and vomited on one occasion.

On 9th October the headache was aggravated, but the temperature was not elevated.

10th October.- Temperature rose to 100°F.

11th October.- Temperature 102·4°F.; the patient was drowsy, but replied readily to questions.

12th October.- She became unconscious in the morning and had retention of urine; no albumin or sugar was present. The temperature rose to 103°F. The cerebrospinal fluid obtained by lumbar puncture was turbid. Polymorphonuclear leucocytes, a few mononuclear cells and erythrocytes were seen in direct films; the cell count was 53 per c.mm., excluding as far as possible the red blood corpuscles.

15th October.- The patient, who remained unconscious from the 12th, died at 8 a.m. on the 15th; temperature 104·8°F.

Autopsy.- On exposure of the brain, a generalised leptomeningitis was disclosed, particularly pronounced

over the left hemisphere. The left olfactory bulb was bathed in pus, and pus was present upon the cerebral surface of the left cribriform plate, the roof of the left ethmoidal cells and the left orbital plate. No inflammatory exudate was seen upon the same areas on the right side of the skull.

No evidence of generalised infection was found in the organs of the chest and abdomen. The patient had a purulent bronchitis.

The frontal sinuses were absent. The right maxillary sinus contained purulent secretion, and the lining mucous membrane was thickened; the left maxillary sinus was normal. A considerable quantity of blood-clot (of post-operative origin) occupied the higher portions of the nasal cavities.

A large block of bone comprising the ethmoidal and sphenoidal air cavities was preserved for microscopic examination. In removing the brain, the left olfactory bulb was retained upon the upper surface of the cribriform plate.

After decalcification, the material was subdivided in the coronal plane into pieces suitable for embedding in paraffin. From each block, serial sections were made in the coronal plane from before backwards.

Report on the Material examined Microscopically.

The series of sections commenced on the plane of the anterior part of the crista galli where the nasal nerves were descending to enter the nasal cavities, i.e., immediately in front of the nasal olfactory area. Further back the sections of the anterior block comprised the olfactory nasal mucosa, the ethmoidal cells, the cribriform plate, and adjacent structures.

1. The Olfactory Mucous Membrane and Ethmoidal Air Cells.- On the right side the secretion in the nasal cavity was scanty and contained very few polymorphonuclear leucocytes. The epithelial lining on the medial aspect of the superior concha was intact and of columnar type, with areas in which the cells were flattened. The mucous membrane was infiltrated by cells, many of them being polymorphonuclear leucocytes. The mucosal glands (Bowman's glands), were active; a few of the acini contained polymorphonuclear leucocytes.

The right ethmoidal cell labyrinth had been opened lateral to the naso-ethmoidal wall and the intervening air-cell walls had been broken up. The cavity thus formed contained blood and a considerable quantity of pus. On some parts of the bony walls

which still remained, the deeper layers of the mucosa were present and in a few areas the lining membrane was intact. These layers were infiltrated by pus, which had also invaded the bony spaces exposed by the operation.

On the left side the nasal secretion was copious and contained a very large number of polymorphonuclear leucocytes. In the more anterior sections, the epithelium covering the superior concha was intact and similar in appearance to that on the right side, but the polymorphonuclear infiltration was more pronounced. More posteriorly, however, the superficial layers of the nasal mucosa on the lateral wall had been destroyed and the underlying bone fractured and displaced by the operation; pus was lying on the surface and infiltrating the deeper layers which remained.

One of the ethmoidal air cells, or a pocket or diverticulum of a cell was present. The cavity was full of coagulated blood and the deeper layers of the mucosa were in situ. The clot had become infected, the infection having started at the lower medial portion where there was traumatic damage to the very thin, osseous, medial wall of the cell. In the contents of the cavity there were several spicules of

bone.

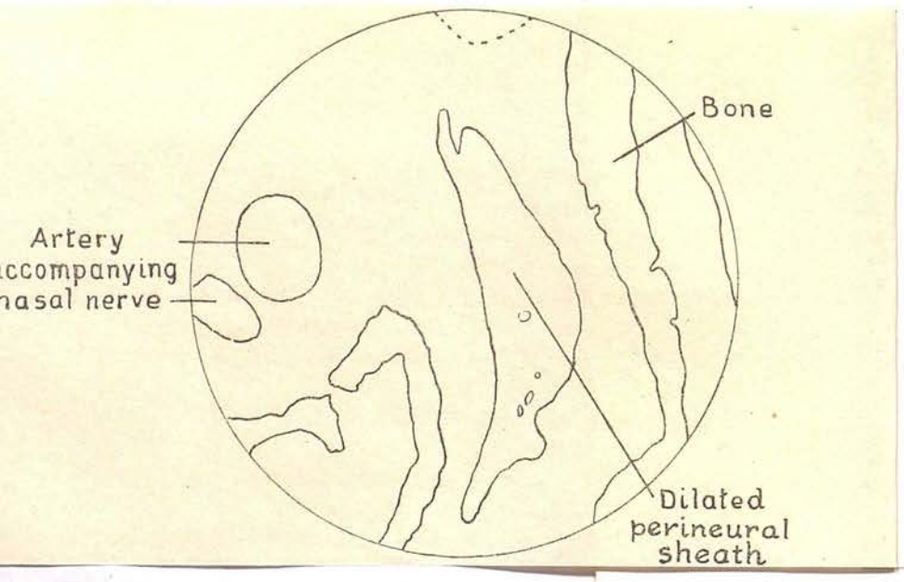
The mucous membrane lining the remaining left ethmoidal cells seen in the sections was intact, and the epithelium was actively secreting mucus; the layers of mucosa were more or less oedematous. No pus was present.

On both sides the blood vessels in the medial naso-ethmoidal bony walls of the air cells were greatly dilated. Considerable osteoporosis was present in the medial wall and roof of the cells on the right side.

2. The Olfactory Nerves.- On both sides the olfactory nerves seen in the sections were composed of only a few nerve fibres, and these were undergoing atrophy with concomitant replacement fibrosis.

The sheaths of all the nerve filaments in the cribriform areas were greatly dilated; those of the smaller nerves in the nasal mucosa were not obvious, the dilatation of the sheaths commencing about the level of the lower bony margin of the cribriform openings.

On the left side one of the dilated sheaths of an olfactory nerve filament contained very numerous polymorphonuclear leucocytes (Fig.73). This nerve ran upwards and backwards through a considerable



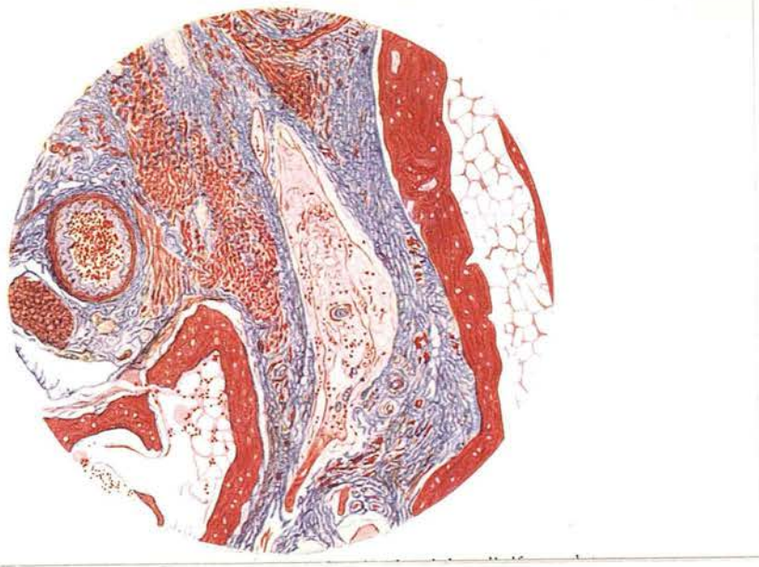
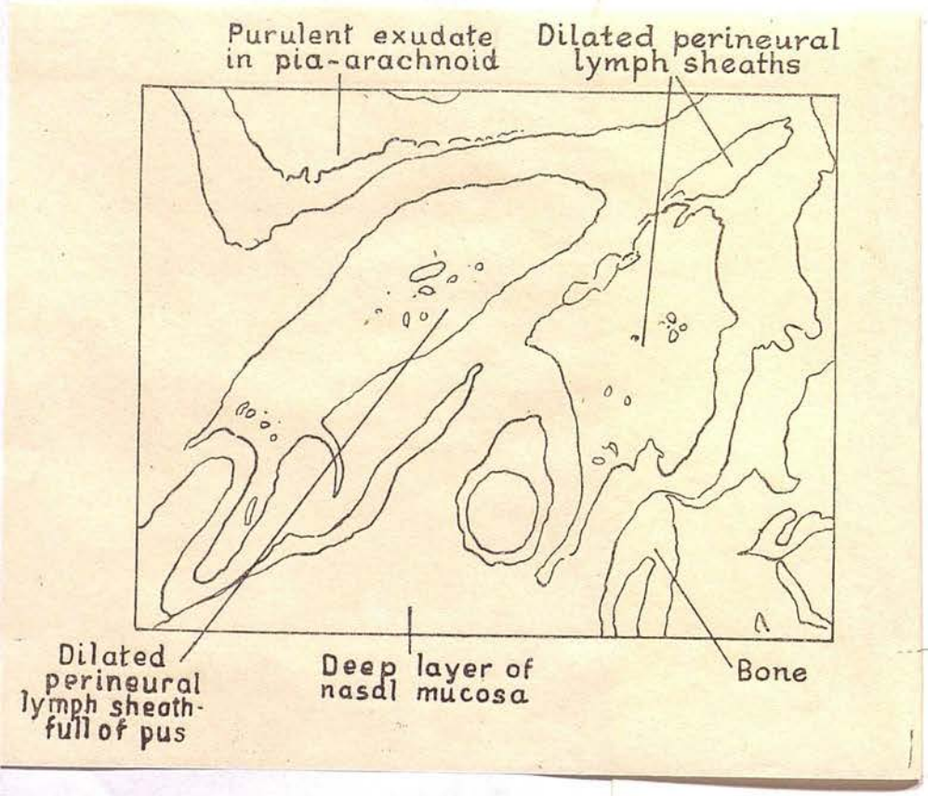


Fig.72.- Coronal section showing an opening in the right cribriform plate. The olfactory perineural lymph sheath is dilated; it contains fluid and a few proliferated endothelial cells.
(Stained by Heidenhain's Azan method.)



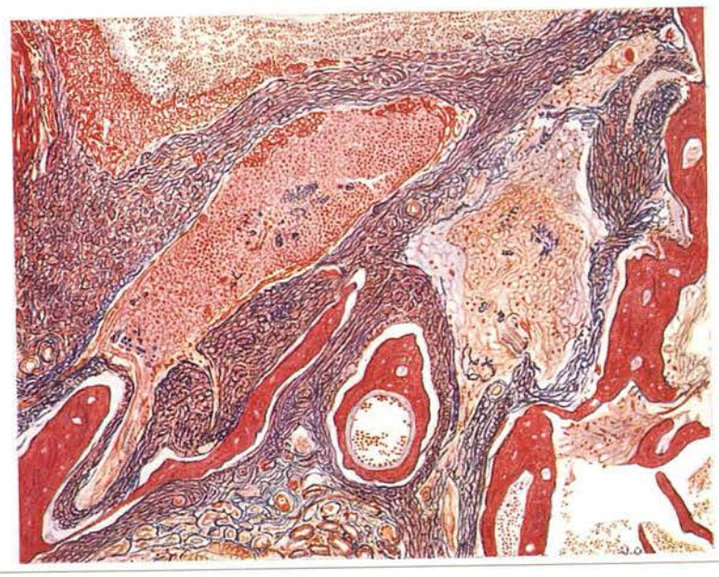


Fig.73.- Coronal section showing openings in left cribriform plate. The olfactory perineural lymph sheaths are dilated, but one only is full of pus.
(Stained by Heidenhain's Azan method.)

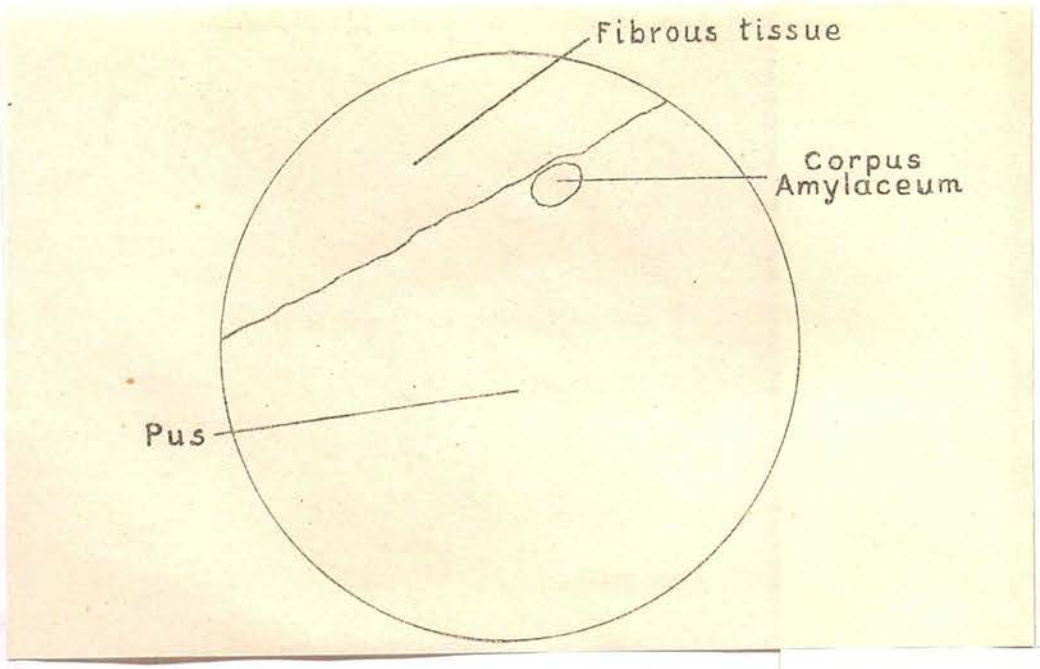
To face page 274.

number of serial sections (170-1000) before piercing the dura mater. At places in the lower part of this perineural sheath the polymorphonuclear leucocytes formed dense aggregations resembling localised abscesses. Higher up, but at a considerable distance from its entrance into the pia-arachnoid spaces, the whole tract was filled with pus as illustrated in Figures 73 and 74. This was continuous with the pus in the pia-arachnoid meshes.

In the dilated perinuural sheaths of the other nerve filaments on both sides, polymorphonuclear leucocytes were only present just before the sheaths became continuous with the pia-arachnoid network. Lower down, in the course of these nerves, the dilated sheaths contained fluid, and larger and smaller, round and oval, proliferated endothelial cells, but only here and there a single polymorphonuclear leucocyte (Figs. 72 and 73).

The Nasal Nerve (Fig. 72).- Throughout the series of sections the nasal nerves were demonstrated. In no situation in their course was there any infection present, either in the perineurium or between the nerve bundles.

3. Sphenoidal Air Sinuses.- The epithelial lining was intact, the mucosa oedematous, and the thin



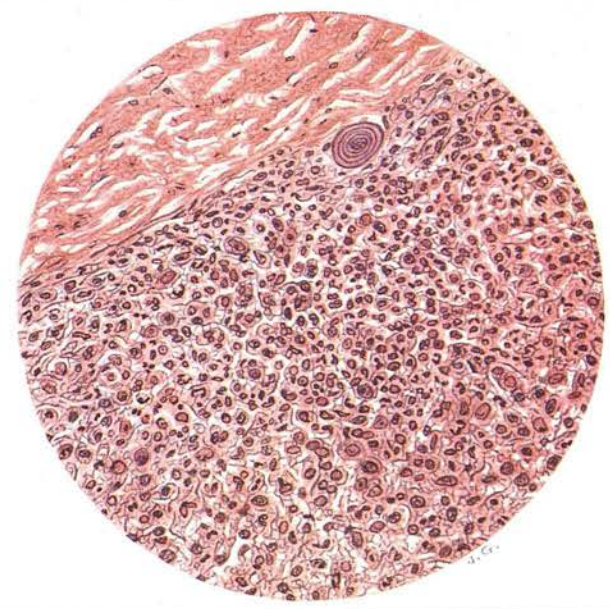
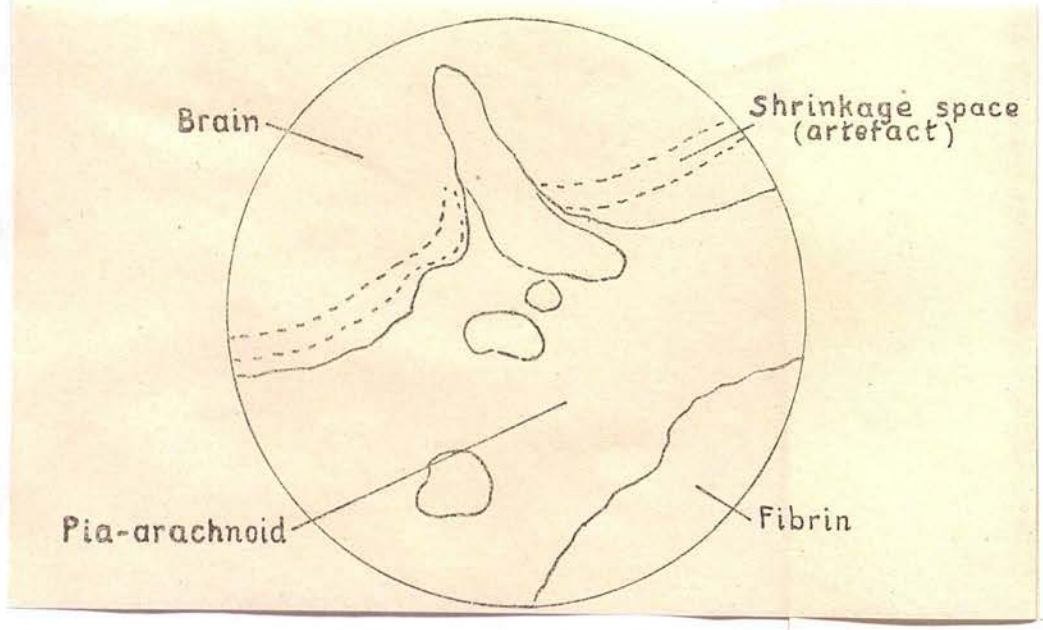


Fig.74.- High-power view of portion of the dilated olfactory perineural lymph sheath filled with pus illustrated in Fig.73.

(Stained by haematoxylin and eosin.)



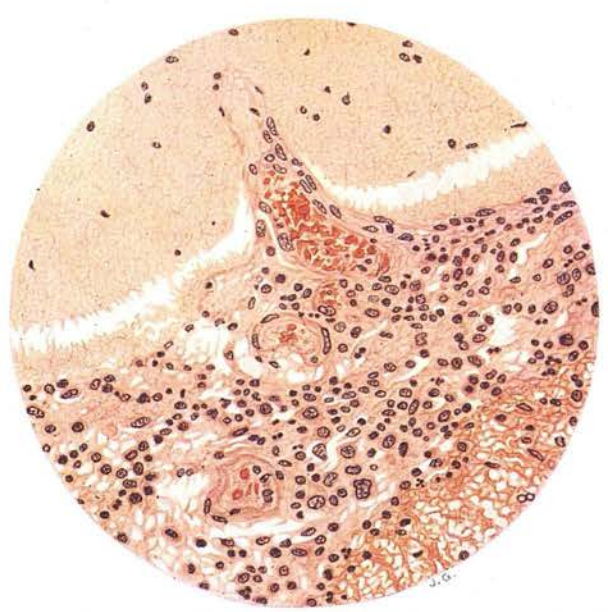


Fig.75.- Coronal section from the under surface of the left frontal lobe showing dilated pial blood-vessels and pus in the leptomeninges.

(Stained by haemotoxylin and eosin.)

To face page 275.

walled blood vessels were dilated. Active diapedesis was occurring through the walls of some of them. The interstices of the mucosa contained fairly numerous smaller and larger, rounded, mononucleated cells, with a certain number of polymorphonuclear leucocytes. Petechial haemorrhages were present. In both sinuses, the polymorphonuclear infiltration was for the most part in the floor, and was more marked in the left than in the right sinus.

The bony walls of both sphenoidal sinuses showed some osteoporotic changes.

4. Cavernous Blood Sinuses.- Both blood sinuses showed post-mortem non-infected clot.

5. The Leptomeninges.- Sections were made from the medial portion of the under surface of both frontal lobes. These included the two olfactory tracts and the overlying leptomeninges.

The smaller pial blood vessels were dilated, and diapedesis of polymorphonuclear leucocytes through their walls was active. The leptomeninges around the olfactory tracts, on the under surface of the brain, and in the various sulci, were densely infiltrated by pus. The pus consisted of fibrin, of large numbers of polymorphonuclear leucocytes and of rounded mononucleated cells (Fig. 75).

Case XXI.

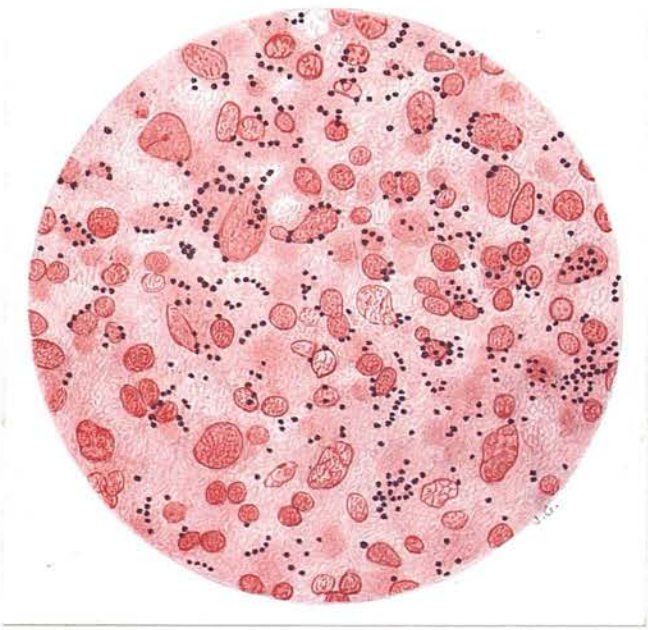


Fig.76.- The illustration demonstrates the micro-organisms in the pus in the dilated lymph sheath of the olfactory nerve filament on the left side at the level of a cribriform opening. The micro-organisms are streptococci and are very numerous.

(The section is stained by Gram's method and counter-stained by dilute carbol fuchsin.)

To face page 276.

6. Bacteriology.- Sections taken from the series described histologically were stained by Gram's method by Professor T. J. Mackie, to whom I am indebted for the following report: "Gram positive streptococci are present in large numbers in the blood-clots lying in the posterior ethmoidal area on both sides. They are present also in the pus in the olfactory perineural sheath on the left side (Fig. 76). The streptococci occur in pairs and short chains which in places are aggregated, giving the appearance of clumps. The micrococci are spherical and non-capsulated. Although conclusive identification of the micro-organisms could only have been made by cultural methods, there can be practically no doubt from these sections that the infection is of pure streptococcal origin.

"In one of the dilated perineural sheaths on the right side, a few Gram positive cocci are observed in the endothelial cells. Streptococci are very numerous in the pus in the pia-arachnoid meshes."

In addition to the infective processes noted in this case, certain senile changes have been observed. Atrophy and disappearance of nerve fibres in the olfactory filaments have been already mentioned. Further, in the osseous nasal septum and walls of the

ethmoidal cells, the bone marrow spaces were filled very largely with yellow marrow. The red marrow cells present were sparsely scattered or collected in the form of small islands. This distribution was due to the replacement of the red marrow by fat cells. Along with these changes, a number of corpora amylacea were present in the upper parts of the sheaths of the olfactory nerves (Fig.74), and in the leptomeninges.

While these manifestations of advancing years are of interest, the writer does not think that they have any direct bearing on the pathway of the infection.

Pathway of Infection.

Since all the olfactory perineural spaces communicating directly with those of the pia-arachnoid, are dilated, it might be maintained that their dilatation in this case was due to the increased pressure of cerebrospinal fluid consequent upon the leptomeningitis.

If such a thesis were correct, dilatation of the olfactory perineural lymphatic sheaths would be met with fairly frequently in cases in which the cerebrospinal fluid is under increased pressure. But in the writer's experience up to the present, this is

not the case; the only examples in the present series in which such dilatation has been found are those associated with infection of the sheaths.

The writer is of opinion, therefore, that the dilatation of the perineural sheaths in this case is active, not passive; that is, it is a reaction to toxins and is comparable to the dilatation of the lymph channels which occurs in association with inflammatory foci in the body generally.

The actual nature and site of origin of the toxins causing the dilatation in this instance cannot be stated with certainty. The writer himself believes that they (the toxins) are a combination of bacteriotoxins elaborated by the micro-organisms in the nose and ethmoidal air cells and of cytotoxins derived from autolysis of damaged and necrotic tissue resulting from the operation and subsequent infection by bacteria. Further, he thinks it probable that the few micrococci present in the endothelial cells have gained entrance to the lymphatic sheaths immediately prior to death and subsequent to the dilatation; the invading micrococci were so few in number that they were ingested by the endothelial cells of the perineural sheaths. Had the patient lived longer and the infection continued, the dilated

sheaths would have contained pus.

Other explanations of the phenomena, however, are possible; for example, it has been suggested to the writer that the dilated sheaths, which at the time of death did not contain pus, had been filled previously by purulent material, and that the condition of these sheaths presented in the histological sections is an end result, the pus having escaped from them. The writer himself is not prepared to accept this explanation, since, firstly, it is difficult to see how evacuation of the pus could have occurred; secondly, if the dilated sheaths had previously contained pus, he would have expected the fine strands and trabeculae demonstrated in the sections to have disappeared, as happened in Case XX, in which the structures in the earliest infected nerve tracts had been destroyed.

In the present case, one of the dilated sheaths, on the left side, is differentiated from all the others by containing pus throughout a great extent of its course; in the higher part, while still distant from its opening into the pia-arachnoid, the sheath is completely filled with purulent exudate. On the other hand, in the sheaths of all the other nerve filaments, pus is present only in the immediate

neighbourhood of their openings into the pia-arachnoid spaces. Undoubtedly, its presence in the latter situations is due to extension downwards from the pia-arachnoid meshes.

But in the case of the nerve on the left side, in which the pus was present throughout a great extent of its perineural sheath, the infection unquestionably passed from below upwards, i.e., primary infection of the pia-arachnoid spaces resulted from an upward extension along it. This is further supported by the fact that the purulent exudation in the leptomeninges was much greater in amount upon, and immediately lateral to, the left cribriform area, as compared to what was present elsewhere on the cerebral surface. This distribution of the pus points to the fact that the purulent leptomeningitis had existed for a longer period at this site, and would imply that the general infection of the leptomeninges had spread from a focus in relation to the left cribriform area.

Summary.- Subsequent to operation on the nasal cavities and ethmoidal air cells, purulent infection of the perineural sheaths of one of the olfactory nerve filaments took place. By direct upward extension this gave rise to primary acute purulent leptomeningitis.

CASE XXII. Nasal Mucous Polypi: Intranasal Operation on the Ethmoidal Air Cells: Purulent Leptomeningitis: Death: Autopsy.

The present case is another example of acute purulent leptomeningitis consequent upon operation on the ethmoidal air cavities and, like Cases XX. and XXI., the microscopical examination of the tissues demonstrates that the infection spread along the perineural sheaths of the olfactory nerves.

C.G., male, aet.57, was seen in the Ear and Throat Department, Royal Infirmary, Edinburgh, on 5th December, 1928, by Dr J.S. Fraser, F.R.C.S.E. I am indebted to him and to Dr W.T. Gardiner, F.R.C.S.E., for the following clinical notes.

The patient complained of intermittent nasal obstruction and a purulent nasal and postnasal discharge.

Examination showed that the mucous membrane of the right middle concha was polypoid and a polypus was blocking the left side. Nothing abnormal was seen in the nasopharynx and choanae. Transillumination revealed both maxillary sinuses dull; the right frontal sinus was clear, but the left was dark.

On 22nd January, the patient was admitted to

hospital and, under local anaesthesia, Dr W. T. Gardiner removed the polypus from the left nasal cavity and the middle concha from each side; both ethmoidal labyrinths and the right sphenoidal air sinus were then opened up.

On the morning of 24th January, the temperature, previously normal, rose to 100°F. and in the evening it had reached 104·2°F. The patient became cyanosed and drowsy, but no head retraction was present and Kernig's sign was not elicited. A lumbar puncture revealed the cerebrospinal fluid to be under increased pressure and cloudy; the cells were 3,324 per c.mm., albumen was slightly increased in amount and the gold reaction gave 0013210000. Direct films of the fluid showed numerous Gram-positive cocci in short chain formation and many pus cells. Later, a fairly profuse growth of a haemolytic streptococcus was obtained.

On 25th January, the typical clinical signs of acute leptomeningitis were obvious and the patient had become unconscious. During the day the temperature reached 105·2°F., and towards evening he developed convulsions and died.

Autopsy.- Permission having been given for the examination of the head, the autopsy was conducted

on 26th January. A diffuse purulent leptomeningitis was present over the anterior three-fourths of the left cerebral hemisphere. A similar condition but not so marked was found on the right side. Pus was present on both sides of the crista galli over the cribriform plate and extending into the middle fossa of the skull. The cribriform area showed no evidence of trauma.

A block of bone was removed comprising the ethmoidal and sphenoidal air cavities, along with the upper part of the nasal cavities and cribriform plate. Examination of the nasal surface of the block showed that an extensive blood clot was present in the area of operation and the right sphenoidal sinus contained a large blood clot.

After decalcification in Parenny's solution, the block of bone removed at autopsy was cut in the coronal plane into pieces of suitable thickness for embedding in paraffin.

Report on the Material examined Microscopically.

Serial sections were made from before backwards in the coronal plane through the roof and olfactory region of the nasal cavities, and the part of the ethmoidal labyrinths still remaining, The series

began in a plane through the middle of the crista galli.

1. Nasal Cavities and Ethmoidal Air Cells.- At the operation, the lateral wall of each olfactory area had been removed almost up to the level of the cribriform plate. On the right side, the superficial layers of the mucous membrane of the roof of the nasal cavity had been detached and removed and on the medial (septal) wall the mucosa had been stripped completely from the underlying bone. On the left side, the olfactory mucosa was intact both on the septal wall and over the roof of the nasal cavity. On both sides the naso-ethmoidal cavities contained a considerable amount of blood-clot, the result of the operation.

Neither the cribriform plate nor the roof of the ethmoidal cells had been fractured.

On both sides, the nasal and ethmoidal mucosa which remained showed acute inflammatory changes, the smaller blood vessels being dilated and the subepithelial tissues being infiltrated by polymorphonuclear leucocytes and larger and smaller mononucleated cells. Numerous haemorrhages had occurred in the mucosal layers; some of these were due to operation trauma; others were an expression of the

inflammatory process.

2. Olfactory Nerves.- In this, as in Case XXI., there was considerable atrophy and disappearance of the olfactory nerve fibres due to senile changes.

In the more anterior sections of the series, the perineural sheaths of a few of the small olfactory filaments in the roof of the right nasal cavity were dilated and contained a number of polymorphonuclear leucocytes. When traced backwards and upwards, these small filaments joined to form a larger nerve; the perineural sheath of the latter was also dilated and contained pus.

On a somewhat more posterior plane, a similar condition was found on the left side; the perineural sheaths of a few olfactory filaments were infected and the pus was traced into the perineural sheath of the larger nerve formed by the union of the smaller filaments. On this side, however, the pus in the perineural sheath of the large olfactory nerve was not so great in amount as on the right side.

On each side, the pus in the olfactory perineural sheath was continuous with that in the pia-arachnoid spaces.

3. The Leptomeninges.- In the sections examined a considerable amount of pus was present in the

groove for the olfactory lobes. Pus was also present in the leptomeninges in relation to the pituitary body and extending laterally.

4. The Sphenoidal Air Sinuses.- In the right sinus the mucous membrane was thickened and some of its blood vessels were dilated; haemorrhages were present in its layers. The columnar epithelium was intact; attached to it were the remains of blood clot. All these changes were the result of operative trauma.

In the left sphenoidal air cavity the mucous membrane of the floor was oedematous. Elsewhere, small localised areas of oedema were present with a certain amount of cellular infiltration, the type of cell being small and large round mononucleated. The lumen of the cavity contained a little mucus.

5. Cavernous Blood Sinuses.- The cavernous spaces on both sides contained only non-infected post-mortem blood clot.

Summary.- Following upon operation for chronic bilateral ethmoiditis, acute inflammation occurred in the nasal mucosa with purulent infection of olfactory perineural sheaths on both sides; as a result of direct upward extension along these sheaths, an acute purulent leptomeningitis developed. Death occurred

three and a half days after the operation and some thirty-two hours after the onset of the signs of meningitis.

CASE XXIII. Chronic Suppuration in the Ethmoidal and Sphenoidal Air Sinuses (Bilateral): Acute Leptomeningitis of Nasal Origin arising spontaneously: Death: Autopsy.

During operation on the olfactory mucous membrane, the perineural sheaths of the olfactory nerves are necessarily opened up; at the same time, should a chronic infection of the mucosa be present, there is always the risk of converting it into an acute inflammation. With such a combination, it will be understood that the acute infection has ready access to the perineural spaces and thence to the leptomeninges. The preceding three cases - Cases XX, XXI, and XXII are examples of this mode of infection of the leptomeninges.

The question presents itself, however, as to whether infection passes by the olfactory perineural sheaths, giving rise to acute purulent leptomeningitis without an immediately preceding operation. That it does so is demonstrated by the present case in which the intracranial complication arose spontaneously from a primary focus in the nasal cavity. Two years previously the patient had undergone a nasal operation which was, however, of no immediate etiological

significance in the development of the leptomeningitis. It is of interest to note that the writer has been unable to find any record of a case investigated microscopically similar to the present one in which no operative factor existed.

A.C.M.B., male, aged 47, had suffered for a number of years from nasal catarrh, and I am indebted to Dr W.T. Gardiner, F.R.C.S.E., for the following brief clinical notes of the case.

On the 21st February 1920, the patient complained of left-sided headache and pain in the left eye. On examination, pus was observed in the left middle meatus and on the vault of the nasopharynx. The left antrum did not illuminate, but, when washed out, nothing was obtained. No further surgical interference was carried out at that time.

On the 23rd February, 1922, an X-ray examination revealed shadowing of the left ethmoidal and sphenoidal cavities and of the left maxillary sinus. The higher cavities on the left side, therefore, were opened by Sluder's technique and the antrum was drained into the nasal cavity. The mucous membrane lining the antrum was considerably thickened. The patient made a good recovery and, later, reported that his condition had much improved. In March

1923, he still complained of some discharge from the nose, but in view of the improvement in his condition no further treatment was carried out.

In February 1924, he became suddenly ill, but forty-eight hours elapsed before the family physician was summoned. The patient had now become unconscious and a diagnosis of meningitis was made. On otoscopy no middle-ear disease was detected, and it was assumed from the previous history that the primary source of the intracranial inflammation was probably in the accessory sinuses.

Autopsy.- Examination of the head only was permitted. Diffuse leptomeningitis was present over the base of the brain. The bone forming the basis cranii in the anterior and middle fossae presented a normal appearance, giving no evidence macroscopically of the source of the meningeal infection. Both frontal sinuses and the left maxillary sinus were normal; the mucosa of the right maxillary sinus was thickened.

Preparation of Material for Microscopic Examination.- A block of bone, comprising the ethmoidal and sphenoidal air-cavities along with the upper part of the nasal cavities and the cribriform plates, was

removed for further investigation.

After decalcification, a coronal section was made just posterior to the crista galli and a second similar section posterior to the cribriform plates. This block of bone included, between the two cuts, the greater part of both nasal cavities with the areas of distribution of the olfactory nerve filaments. A second block contained the crista galli. Both were cut in serial sections.

Report on the Material examined Microscopically.

1. The Ethmoidal Air-Cells.- In both nasal cavities the naso-ethmoidal or medial wall of the ethmoid labyrinth was absent, with the exception of the extreme upper portion on the left side. The absence of this wall in the left nasal cavity was the result of the intranasal operation performed two years previously. On the right or non-operated side the corresponding wall had completely disappeared, this being due to a chronic cario-necrotic process, and in a small area of the roof the process had completely eroded the bone. There was no infection of the overlying dura mater in this area.

The naso-ethmoidal cavities thus formed on both sides contained pus. The mucous membrane was

thickened; it was infiltrated by polymorphonuclear leucocytes and large and small mononucleated cells. For the most part the epithelial covering was present, but in some areas it, along with the subjacent tissue, was necrotic. In addition, a small abscess was present in the mucous membrane of the lateral wall of the right naso-ethmoidal cavity.

In the lateral or orbito-ethmoidal walls, osteoclasts were active in many of the Haversian spaces, while osteophytes had formed in the periosteal layer of the mucous membrane.

The walls of many of the arteries in the deeper mucosa lining the roofs of the cavities were thickened.

In the series of sections there was no evidence that the osseous floor of the anterior cranial fossa had been fractured at the operation two years previously.

2. The Olfactory Nerves.- In both nasal cavities numerous filaments of the olfactory nerves were present in the mucous membrane of the nasal septum and in the small portion of the naso-ethmoidal wall remaining on the left side. On this side the perineural sheath of a branch of one of these nerve filaments lying in the upper part of the septal

mucosa was dilated and infiltrated by pus. The sheath of the filament itself showed this to a marked degree. In serial sections the pus in this sheath was continuous with that present in the pia-arachnoid meshes. None of the sheaths of the remaining olfactory nerves present in the sections were infected.

The condition of the infected olfactory perineural sheath is not illustrated in the present instance, as it is essentially the same as that shown in Fig.61, Case XX.

3. The Cavernous Blood Sinuses.- None of the blood spaces of the cavernous sinuses contained antemortem thrombus.

Summary.- Microscopic examination demonstrated chronic inflammation of the mucous membrane lining the upper part of both nasal cavities. On the left side, purulent infection of the perineural sheath of one of the olfactory nerve filaments had occurred. By direct upward extension this had given rise to acute purulent leptomeningitis. Owing to the length of time which had elapsed between the nasal operation and the infection of the leptomeninges, the operative factor could not have been directly responsible for the infection of the olfactory perineural sheath.

In considering the factors which may have an indirect bearing upon the onset of leptomeningitis, the question naturally arises as to whether alteration in the normal anatomical arrangements of parts influences the spread of infection. In other words, was the nasal operation performed two years previously a remote etiological factor in this case?

The literature contains a considerable number of instances in which an antecedent trauma, operative or otherwise, or a defect, congenital or acquired through disease, was an etiological factor in the transmission of infection from an extracranial focus of inflammation to the leptomeninges. In these cases, however, the trauma or the defect was the direct factor responsible for the development of the leptomeningitis. The only published case the writer has been able to find having a bearing upon the remote effect of trauma is described by Fujisawa and quoted by Dahmann and Müller. A girl, aged 10 years, fell from a two-storied building, fracturing the left side of the frontal bone. Bleeding from the nose and mouth was associated with the escape of cerebral tissue. Two months later the child had completely recovered, remaining well for one year and three months. She then developed an acute purulent basal

meningitis which was rapidly fatal. Autopsy revealed an old fracture in the frontal bone involving the cribriform plate. As no microscopic examination was made, the actual pathway of infection was not demonstrated.

In the instance now recorded, in contrast to the above, no fracture had occurred.

In point of fact, however, our knowledge of the factors concerned in local immunity is so deficient that it is impossible to estimate in the present case the influence, if any, of the previous intranasal operation upon the infection of the olfactory perineural sheath.

VII. THE PATHWAY OF INFECTION AS THE DETERMINING FACTOR OF THE INTRACRANIAL LESION.

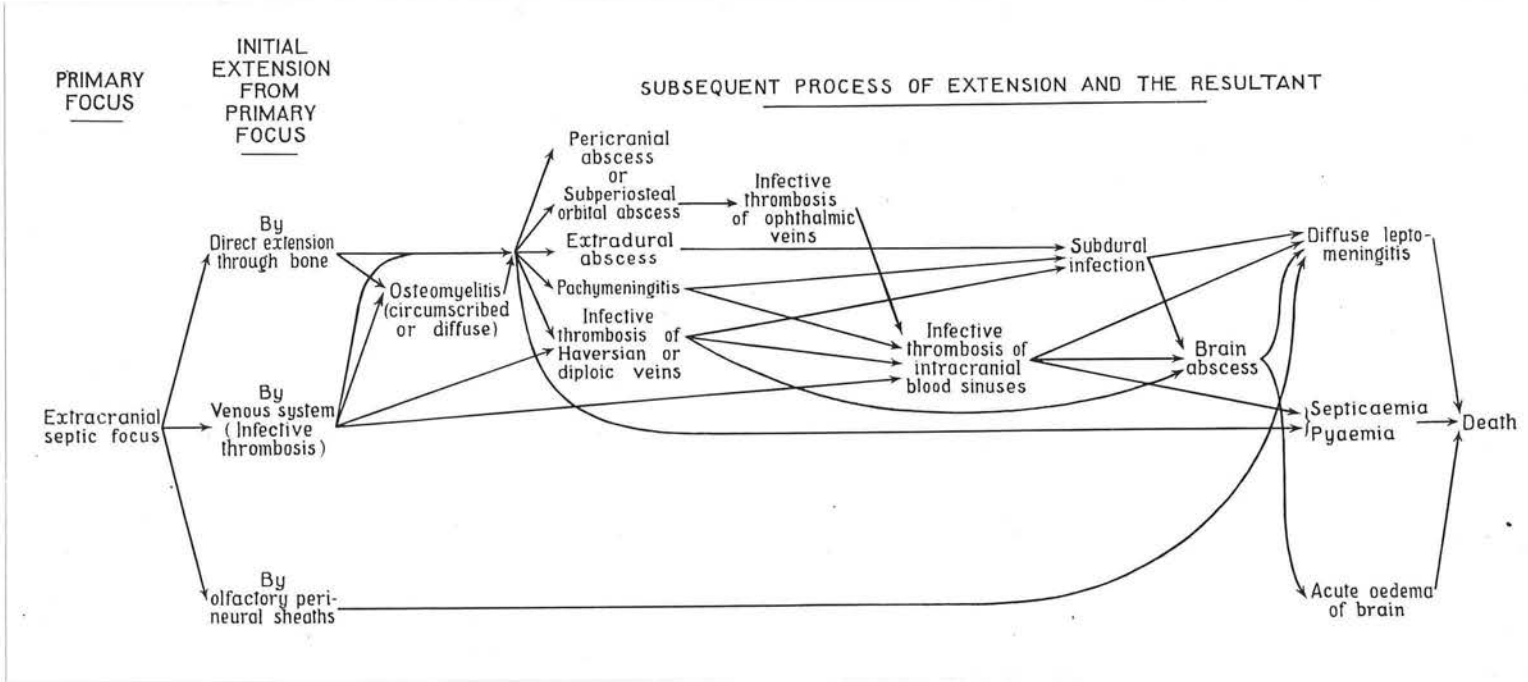


Fig.77.- Schema.

Note 1. The olfactory perineural sheaths cannot properly be considered lymphatics (see page 2).

Note 2. The lymphatics as a pathway for the spread of infection from the primary focus do not occur in the above schema since there is no direct relationship between them and the intradural structures; consequently infection cannot reach the dural blood sinuses, the leptomeninges, or the brain and spinal cord by the lymphatic vessels alone (see pages 1 et seq.).

To face page 297.

VII. THE PATHWAY OF INFECTION AS THE DETERMINING FACTOR OF THE INTRACRANIAL LESION.

Fig.77

From the preceding sections, it will be seen that when the infection passes from an inflammatory focus in the face, nose, or nasal accessory sinuses to the intracranial structures by the blood stream, the initial thrombosis of mucosal or cutaneous veins gives rise to infective thrombosis of the cavernous blood sinus. The infection may pass direct to the blood sinus by one of the larger tributary veins or, on the other hand, during the course of its extension, an infective thrombosis of Haversian or diploic veins may occur and from thence the blood sinus may be infected. In the latter instance, the infective thrombosis of the osseous vein may be associated with osteomyelitis, circumscribed or diffuse; this may be a preliminary stage of, or a subsequent complication of, the progress of the infection. Lastly, infection of an osseous vein may give rise directly to acute purulent meningitis.

When the extension of the inflammatory process

passes by way of the olfactory perineural sheaths, a leptomeningitis is set up, at first localised to the cribriform area, but soon distributed diffusely.

When the infection is propagated by direct extension through the bone and dura mater, a diffuse leptomeningitis is usually the final result. In these cases, the typical stages of the process are, firstly, an osteomyelitis with or without an extradural abscess, then pachymeningitis, subdural infection, and finally, diffuse leptomeningitis. When the spread of a purely direct extension is slow, however, while the process is proceeding through the dura mater, adhesions may be set up between the cerebral aspect of this membrane and the membrana superficialis cerebri to which is welded the deeper or pial layers of the pia-arachnoid membrane. In this case, therefore, when the micro-organisms reach the pia-arachnoid space, they may be localised by the adhesions and a subdural abscess formed. Further extension of the infective process may occur and a cerebral abscess result. The natural complications of cerebral abscess are, firstly, a diffuse leptomeningitis due to so-called leakage of the pus into the pia-arachnoid spaces or, secondly, acute oedema cerebri. Finally, in the progress of infection by

direct extension through the dura mater, the wall of a dural blood sinus may be involved and septic thrombosis of the latter structure occur.

While these are the more direct paths by which infection may reach the intracranial structures, other complications may arise during the advancing process and may determine the further route of the septic process and consequently the type of intracranial involvement.

Thus, it has been mentioned above that circumscribed or diffuse osteomyelitis may occur as a result of infective thrombosis of mucosal veins, or as a stage in the process of direct extension through bone. By whichever method septic osteomyelitis is brought about, this complication may give rise not only to infective thrombosis of Haversian or diploic veins, to extradural abscess, and to pachymeningitis, but to a pericranial abscess. If this last complication be in relation to the orbital walls, in other words if it be a subperiosteal abscess, an infective thrombosis of the ophthalmic veins may follow, and this in turn may lead to infection of the cavernous blood sinus.

Lastly, osteomyelitis and infective thrombosis of the cavernous blood sinus gives rise to

septicaemia or pyaemia.

Whatever may be the intermediate complications in the passage of the infection from the extracranial focus, the possible ultimate results are diffuse leptomeningitis, septicaemia and pyaemia, or acute oedema of the brain.

The initial pathway by which extension from the primary focus may occur, with the subsequent process and resultant complications, is summarised in the subjoined schema (Fig.77).

VIII. PROGNOSIS OF INTRACRANIAL INFECTIVE LESIONS FROM THE PATHOLOGICAL STANDPOINT.

VIII. PROGNOSIS OF INTRACRANIAL INFECTIVE LESIONS FROM THE PATHOLOGICAL STANDPOINT.

It is beyond the scope of this Thesis and outside the knowledge and experience of the writer to consider in clinical detail the prognosis and treatment of the various complications which may arise in the course of a progressive infection. The purpose of pathology, however, is to determine the processes which constitute disease and their nature; from an understanding of these phenomena, certain general deductions can be drawn as to the prognosis which may be given by the clinician at any particular stage in the development of the infection.

Attention has been directed (pg.250) to the fact that the dura mater is a structure which, in virtue of its component elements, is not only an efficient barrier to the passage of infection, but that its resistance in this respect is much greater than that of the bones forming the skull. On these grounds it would be concluded that, in regard to the further stages of the process towards death on the one hand and recovery on the other hand, infection of the structures within the dura mater is of a very

different nature to infection limited to the parts external to that barrier.

This conclusion, based on anatomical and pathological considerations, is borne out by clinical experience. So long as the infection is external to the dura mater, recovery by surgical intervention is not only possible but usual. For example, the presence of an extra-dural abscess does not of itself imply a bad prognosis. When it is the ultimate stage of the progress of infection at the time of operation, it is of surgical significance only in that it indicates, firstly, that the bone is infected and, secondly, that the infection is throughout its whole thickness and has reached a position from which its further action may be upon the resistant dura mater. When there is evidence that infection of bone has occurred, the prognosis is graver, for reasons already given (pgs. 95 and 251), than if no affection of the osseous structures is present.

The prognosis is very different, however, if the infection has reached the dural blood sinuses, the leptomeninges, or the brain. Certainly many cases of recovery have occurred after surgical operation on a chronic subdural abscess or on a chronic abscess of the brain; on the other hand, in both conditions,

post-operative infection of the leptomeninges is a not infrequent cause of a fatal issue, and in the case of a cerebral abscess, acute oedema of the brain occurs not uncommonly after the pus has been evacuated by surgical operation.

A few cases of recovery from infective thrombosis of the cavernous blood sinus have been recorded, one of which is included in the present series (Case XIII); cases have been published in which the patient recovered from diffuse leptomeningitis of otitic origin; and the writer is not prepared to maintain that a case of acute oedema of the brain never has recovered or never will recover. Recoveries, however, from the three ultimate possibilities of intracranial infection in the area with which this Thesis mainly deals - cavernous sinus thrombosis, leptomeningitis, and acute oedema cerebri due to brain abscess - are clinical rarities. In the overwhelming majority of instances, the termination of these three complications is death.

It is the universal custom of surgeons to include in their statistics extra-dural abscess as an intracranial complication. While this is justifiable on terminological grounds, it must be clearly understood and recognised that the important dividing

barrier is the dura mater and not the cranium. Failure to grasp this important fact must lead to a totally false conclusion being drawn from published statistics as to the probable termination of intracranial infection. Once infection has progressed through the dura mater into the cavernous or other dural blood sinus, into the leptomeninges, or into the brain, the case, so far as the prognosis is concerned, is in an entirely different category to what it was before that barrier had broken down. Statistics of various surgical cliniques give a percentage of recoveries from intracranial infections which at first sight is surprisingly high, but on analysis of the figures, it is found that a large number of the recoveries are cases of extra-dural abscess.

IX. REFERENCES.

IX. REFERENCES.

André, M.: Contribution à l'étude des lymphatiques du nez et des fosses nasales. Thèse de Paris. 1905.

Ayer, J.B. and Soloman, H.C.: The Human Cerebro-spinal Fluid. New York, 1926.

Barbier, H.et Lebée,L.: Infection secondaire d'une méningite cérébro-spinale à meningocoque B. par le streptocoque, Bull. Soc. de pédiat. de Paris, 1922, tome 20, p.108.

Brunner, H.: Beiträge zur Kenntniss der otogenen Cavernosusphlebitis, Monatschr. f. Ohrenh., 1926, Jahrg. 60, S.2.

Burger, H.: Die endokraniellen Komplikationen der Nasennebenhöhlenentzündungen, Handbuch der Hals- Nasen- Ohrenheilkunde, Berlin, 1926.

Clark, W.E. le Gros: An anatomical investigation into the routes by which infections may pass from the nasal cavities into the brain. Reports on Public Health and Medical Subjects, No. 54, London, 1929.

Dahmann, H. und Müller, H.: Lamina-cribrosa-Defekt und Meningitis, Ztschr. f. Laryngol., Rhinol. u. Otol., 1925, Bd.13, S.247.

Druss, J.G.: Intracranial complications associated with disease of the sphenoid bone, Arch. Otolaryngol., 1929, vol.10, p.39.

Eagleton, Wells P.: Cavernous Sinus Thrombophlebitis, New York, 1926.

Eicken, C. von: Unsere Ehfahrungen über Komplikationen bei Erkrankungen der Nasennebenhöhlen. Verein deutscher Laryngologen, 8, Juni 1908. Centralbl. f. Laryngol., Rhinol., u. verwand. Wissensch., 1909, 25 Jahrg., S.85.

Embleton, D. and Peters, E.A.: Cerebro-spinal fever and the sphenoidal sinus, The Lancet, 1915, vol.1, p.1078.

Fitzgerald, J.G.: Mixed infection (meningococcus and pneumococcus) meningitis, J. Amer. Med. Assoc., 1918, Vol.71, p.969.

Fraser, J.S. and Dickie, J.K.M.: An analysis of 123 consecutive cases in which operations were performed for the relief of the mastoid, labyrinthine and intracranial complications of

suppurative otitis media,: J. Laryngol., Rhinol., and Otol., 1912, vol.27, p.133.

Fujisawa, K.: Ein Fall von Spät-Meningitis nach Schädelverletzung, Münch. med. Wchnschr., 1901, 48 Jh., S.1784.

Gerber, P.H.: Die Komplikationen der Stirnhöhlenentzündungen, Berlin, 1909.

Hajek, M.: Beiträge zum Studium des Infectionsweges bei rhinogenen Gehirnkomplikationen, Arch. f. Laryngol. v. Rhinol., 1906, Bd.18, S.290.

Key, A. und Retzius, G.: Studien in der Anatomie des Nervensystems, Stockholm, 1875.

Killian, G.: Handbuch der Laryngologie und Rhinologie, von Dr P. Heymann, Hf.2, S.1128, Vienna,1900.

Levinson, A.: Cerebrospinal Fluid in Health and Disease, 3rd Ed., London, 1929.

Luc, H.: Leçons sur les Suppurations d'l'Oreille Moyenne et des Cavités Accessoires des Fosses Nasales, Paris, 1900.

Macewen, William : Pyogenic Infective Diseases of the Brain and Spinal Cord, Glasgow, 1893.

McKenzie, Dan : Diffuse osteomyelitis from nasal sinus suppuration, J. Laryngol. and Otol., 1913, vol.28, pp.6,79,129.

Manasse, P.: Ueber orbitale und cerebrale Komplikationen bei akuten Nebenhöhleneiterungen. Verhandl. d. Ver. deutsch. Laryngol., Würr.26, 1911, S.621.

Miodowski, F.: Komplikationen nach submukoses Septumresektion, histologische Untersuchungen über ihre Genese. Verhand, d, III Internat. Laryngol. Kongress, Teil 2, S.179, Berlin,1912.

Ortmann, P.: Der Diplococcus pneumoniae bei eitriger Meningitis, Virchows Arch. f. path. Anat., 1890, Bd. 120, S.117.

Sokolow, P.: Der Canalis craniopharyngens, Arch. f. Anat. u. Physiol., Anat. Abth., 1904, S.71.

Sternberg, H.: Ueber den zerebralen Infectionsweg bei Stirnhöhleneiterung und makroskopish intaktem Knochen, Monatschr. f. Ohrenh., 1923, Bd.57, S.44.

Stewart, J.P.: The histo-pathology of mastoiditis, J. Laryngol. and Otol., 1928, vol.43, p.689.

Schultz, A.: Der Canalis craniopharyngeus persistens beim Menschen und bei den Affen, Morphol. Jahrb., 1917, Bd.50, S.417.

Turner, A. Logan : The Accessory Sinuses of the Nose, Edinburgh, 1901.

Turner, A, Logan, and others : Diseases of the Nose, Throat and Ear, Bristol, 1927.

Wittmaack, K.: Die Mastoiditis, Handbuch der speziellen pathologischen Anatomie und Histologie, Gehörorgan, Berlin, 1926.

Yates, A. Lowndes : The condition of the accessory sinuses in encephalitis lethargica, J. Laryngol. and Otol., 1925, vol,40, p.646.

Zwillinger, H.: Experimentelle Untersuchungen zur Mechanik der intrakraniellen und zerebralen Komplikationen der Stirnhöhlenentzundungen, Arch. f. Laryngol. u. Rhinol., 1914, Bd.28, S.271.